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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1926

ORIGINAL ARTICLES.

TERTIARY SYPHILIS OF THE LIVER.*

By Thomas McCrae, M.D., F.R.C.P. (Lond.),

and

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Philadelphia.

(From the Jefferson Medical College, Philadelphia.)

In a previous communication[1] this subject was discussed, based on a study of 56 cases, and at the present time the series is extended to 100 cases which have been studied in the hospital service and practice of the senior writer. The total number of this series is chosen as a convenient one. No case has been included which seemed in any way doubtful. The time has not come to decide whether the more intensive treatment of syphilis in the earlier stages has resulted in a decrease in the later involvement of the liver, but the impression obtained is that this has not been accomplished. The use of arsenic preparations in treatment has added to the danger of hepatic syphilis if the patient with this lesion falls into the hands of one who does not know of the harm that may result from such treatment. Further observation has emphasized the importance of the prompt diagnosis of hepatic syphilis. Recognized in time, the therapeutic results are excellent if proper treatment is given. Unrecognized and untreated, the results are serious in many cases; some undoubtedly recover, so far as the acute

* Read before the Association of American Physicians, 1926.

[1] McCrae, T.: Tertiary Syphilis of the Liver, Am. J. Med. Sci., 1912, **144**, 625.

features are concerned, without any marked treatment as proved by autopsy findings.

Etiology. The contributing factors are as follows:

Age. The distribution by decades is as follows:

Decades.	No. of cases.	Decades.	No. of cases.
1 to 10	1	41 to 50	25
11 to 20	4	51 to 60	10
21 to 30	20	61 to 70	5
31 to 40	35		

The 5 cases below the age of twenty years were regarded as congenital syphilis, the ages being three, thirteen, sixteen, eighteen and nineteen years. The oldest patient in the series was seventy years of age.

Color. There were 70 white and 30 colored, and the relatively high proportion in the colored race is found in Philadelphia, as in Baltimore. It is probably due to the higher incidence of syphilis among the colored.

Sex. There were 66 males and 34 females. The proportion of colored females is less striking, 14 of 34 cases, than in the earlier series, in which it was 10 among 15 females. The greater use of alcohol by males may account partly for the difference.

Alcohol. Excluding the 5 patients below the age of twenty years, of the remaining 95, there were 55 cases in which there was a clear history of the steady use of alcohol. In only 5 was the record of slight use; 27 were described as moderate drinkers and 23 had drunk to excess. The influence of alcohol as a contributing factor in hepatic syphilis seems well established, but this does not mean that syphilis is added to an alcoholic cirrhosis.

History of Syphilis. In the congenital cases there was a fairly clear history in all. In the acquired cases there was a definite history of a primary infection in 35; in 22 others there were strongly suggestive features in the history. The time which had elapsed between the primary lesion and the hepatic disease varied from eighteen months to twenty-five years. An effort was made to obtain information as to features of the secondary stage but, as is usually the case, the information was not satisfactory. We have the impression that the secondary manifestations were not marked; at any rate the patients did not appear to have noted them very often.

Clinical Features. *Complaint.* The principal complaints made by the patients are very varied. Taking those which stood in relation to the hepatic lesion, the most common complaint was swelling of the abdomen in 46. Pain in the abdomen, usually referred to the upper part, came next with 37 cases. Other complaints were jaundice in 8, shortness of breath in 16, loss of weight or strength in 7, edema of the legs in 7, vomiting in 5, fever in 2

and chills and fever in 5. Some patients complained of two or more of these.

Past History. The features which stand out in this are of importance, as they often lead to a wrong diagnosis and in some points should suggest the diagnosis. The most important of them are as follows: *Loss of weight* is common and varied from 15 to 50 pounds in 54 cases. The occurrence of *fever* had led to many diagnoses. When associated with chills malaria had been diagnosed and quinine given for long periods. In 1 patient chills and fever had existed for eighteen months. A persistent fever without recognized cause had led to the diagnosis of tuberculosis in some instances, and 1 patient had spent nearly two years in a tuberculosis sanitarium. The fever disappeared in two days after iodide was begun.

Previous Ascites. This is of particular interest, as it may give a clue to the diagnosis. In 10 patients of the series there had been previous ascites which required tapping, after which the ascites disappeared. The intervals between the previous tapping and the present illness varied from some months to eleven years. In these intervals there had been marked improvement. From the histories these patients appeared to have had reasonably good health in the intervals between the attacks of ascites. The maximum number of previous tappings was 27. This patient had been tapped 11 times in one year eleven years before and 16 times in the next year, 200 liters of fluid being removed. Unless there is some other clear explanation for such a history, it should suggest hepatic syphilis very strongly. Probably most of the patients with supposed portal cirrhosis, other than those with marked chronic local peritonitis, who have recovered really had hepatic syphilis. It is altogether possible that some cases of ascites which recover without tapping belong to the same class, although not as easily recognized.

The duration of symptoms when the patients came under observation varied from one month to eleven years. It was three months or less in 25 cases, three to six months in 15 cases, six months to one year in 18 cases, from one to two years in 16 cases, about two years in 8 cases, three years in 5, four and seven years in 1 each and eleven years in 1. A striking feature in the cases of longer duration is the variation in the symptoms; some patients had periods of fair health alternating with illness. Of special interest in this connection is the history of previous ascites.

Abdominal Features. The most striking was abdominal swelling, due in the majority to ascites but in some to the tumor of the liver. Abdominal pain was common, variously referred but usually to the upper abdomen. Gastric disturbances, such as discomfort and vomiting, were fairly common, and in some cases there had been hematemesis and melena. In some cases the gastric hemorrhage had been severe.

An interesting point arises as to the rapidity of enlargement of the liver. There is only 1 case in the series in which we have definite information. A male, aged forty-two years, was admitted, complaining chiefly of abdominal pain, on January 3, 1919. Duodenal ulcer was suspected and he was carefully studied. There was no jaundice and there was no enlargement of the liver or spleen. A diagnosis of ulcer was not made definitely. He was discharged on January 22, feeling very much better. He was readmitted on April 25, complaining of abdominal pain and distention. He never showed distinct jaundice. The liver was much enlarged, the edge in the right nipple line being 6 cm. below the costal margin and in the midline reaching almost to the navel. In the epigastrium there was a large, rounded prominence. The liver was everywhere smooth. The spleen was palpable; there was no ascites. The Wassermann reaction was strongly positive. He was given mercury and iodid; rapid improvement followed, and within three weeks the liver showed very little enlargement. The size of the spleen was reduced and his blood count had risen from 4,000,000 to 5,000,000 cells. In this patient the enlargement of the liver and spleen had occurred within a period of three months.

Abdominal Pain. This was a striking feature in 61 cases. The situation of the pain varied somewhat; in 23 it was referred to the epigastrium and in 19 it was more or less general; in 9 cases it was referred particularly to the upper right quadrant; in 4 it was described as being localized in the liver; in 4 it was referred to the back. One patient referred it to the region of the navel and 1 to the upper left quadrant. The severity of the pain was so striking in some cases that this had suggested an acute inflammatory lesion and several of the patients had been operated on with the expectation of finding acute cholecystitis. The associated tenderness may be so marked that a satisfactory examination is difficult.

General Condition. A striking feature was *emaciation*, which was marked in 48 cases, and in some it was extreme. A number of other patients had lost some weight but could not be described as emaciated. The appearance of many of the patients suggested severe illness. Jaundice was present in 40 cases; the degree varied from slight to marked jaundice, the color of several being greenish-yellow. A striking feature is the rapidity with which the jaundice clears under treatment.

Fever. There was some elevation of temperature in 81 cases of the series. This is a point of some importance in reference to diagnosis, as the persistence of fever had led to tuberculosis, hepatic abscess or cholecystitis being suspected in some cases. A number of the patients were sent to the hospital with these diagnoses. The temperature showed constant elevation in about two-thirds of the cases. In the majority this was not very high, the records being 99° to 101° F. In some cases it was steadily between 100° and

102° F. In the other cases the temperature was not constantly elevated but rose each day. In the majority the highest point was not over 102° F., but in 3 cases it rose to 103° and 104° F. In some cases these elevations were accompanied by chills.

An example of the difficulties in diagnosis is as follows: A male, aged twenty-nine years, was admitted to the surgical service, complaining of abdominal pain. He stated that four years before he was operated upon for gall stones and a year later had a second abdominal operation, the reason for which he did not know. He had used alcohol moderately and denied syphilis. His present illness began a week before with fever, chills and pain in the region of the liver. With leukocytosis and severe pain and tenderness in the upper right quadrant of the abdomen, exploration was done and a mass of adhesions found with no sign of the gall bladder. The liver was found studded with whitish areas; a portion of one which was removed showed some cirrhosis and necrosis. The wound healed well but he continued to have fever and chills, and after one chill the temperature rose to 106° F. When first seen by one of us at this time, there was jaundice and the liver was much enlarged and hard. The spleen was greatly enlarged. He was given iodide but it was six days before the temperature reached normal, where it remained. He gained rapidly, put on considerable weight, the jaundice disappeared and the liver and spleen decreased greatly in size.

The influence of treatment on the fever was very marked in almost all the cases in which fever was present. In 2 patients the temperature fell to normal in twenty-four hours and remained there, but the most common period required was forty-eight hours, as seen in 14 cases. In 10 cases three days were required, and in 9 other cases the temperature reached normal in six days or less. This followed the administration of potassium iodide alone in the majority of cases; in some mercury was given also, but the most striking results were obtained with potassium iodide alone (Fig. 1).

Blood. The average count in 66 cases was: Hemoglobin, 70 per cent; red cells, 4,300,000 per c.mm.; leukocytes, 8400 per c.mm. In 20 cases the leukocytes were over 10,000 per c.mm., the highest count being 18,400 per c.mm. In only 4 cases was the red cell count below 3,000,000, the lowest being 2,700,000 per c.mm. in an uncomplicated case. In 1 patient with pernicious anemia and hepatic syphilis the red cell count was 940,000. In 16 cases the count was between 3,000,000 and 4,000,000. The differential count showed some variation in certain cases, but there were no striking constant peculiarities.

The *blood Wassermann reaction* in 41 cases of the last series in which a satisfactory result was obtained was negative in 8 cases. The evidence suggests that it is negative in a larger proportion of cases of hepatic than in other forms of visceral syphilis.

Ascites. In 42 cases this was present and usually the fluid was large in amount. Tapping was done in 21 cases. This may seem a small proportion, but one of the striking features is the rapid disappearance of the ascitic fluid under proper treatment without tapping being required. The rapidity with which the ascitic fluid can be absorbed is remarkable. In a patient with marked ascites within a week or ten days after the administration of iodide is begun it may be difficult to demonstrate any ascites. In 7 of the 21 patients one tapping was sufficient, 7 were tapped twice, 3 required to be tapped three times and 1 each was tapped, five, six and thirteen times. The amount removed at one tapping varied from 2.5 to 22 liters. This last figure seems very large; the patient was admitted twice within six months and was tapped once on each admission, the amounts removed being 19 and 22 liters. She

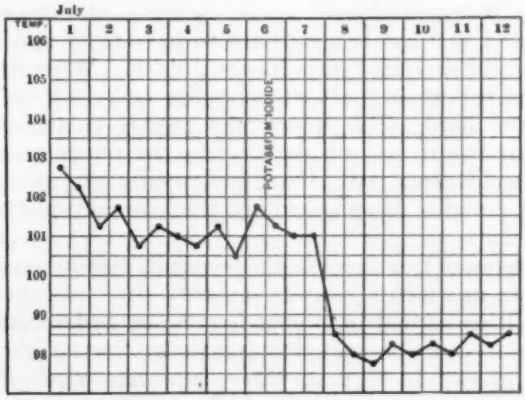

FIG. 1.—Showing the effect of potassium iodide on the fever.

presented a remarkable appearance before each tapping and after it the improvement was striking. She was a colored woman, who refused to remain in the hospital long enough to receive thorough treatment. The specific gravity of the ascitic fluid varied from 1008 to 1020 and the albumin content from 8 to 40 gm. per liter. The predominant cells were small lymphocytes. The Wassermann reaction was positive in the ascitic fluid in 4 and negative in 3 cases. In 1 of them it was positive in the ascitic fluid and negative in the blood.

Spleen. This was palpable in 50 cases, in the majority the enlargement being marked, in some the edge being several inches below the costal margin. In 16 other cases the area of dulness was increased. The spleen was always hard and firm; in no instance was any irregularity felt; in 1 case a splenic gumma was found at autopsy.

If the enlargement of the spleen is marked a diagnosis of splenic anemia may be made, as was the case in several of the series when admitted to the hospital. A striking instance is as follows: A white female, aged thirty years, came complaining of an abdominal tumor. She had been very healthy as a rule. There had been one miscarriage shortly after her marriage. She dated her illness to five years before, when menstruation stopped. She consulted a physician who found a greatly enlarged spleen. About this time she had a period of fever with occasional chills, for which no cause was found. There was a progressive loss of weight from 140 to 113 pounds, and she was considered to be seriously ill. She saw a well-known consultant who made a diagnosis of splenic anemia and stated that she had only a short time to live. He had the courage of his opinions as he gave the husband a signed statement to this effect, which was produced four years later. In the years following she had a good deal of gastric disturbance and a curious pigmentation appeared which was fairly general. She had no menstrual period during the five years.

Examination showed emaciation and brownish pigmentation with some jaundice. The veins on the surface of the abdomen were dilated. The liver was somewhat enlarged and the edge was about 5 cm. below the costal margin. It was hard, smooth and not tender. The spleen was enormous, extending to the navel in the midline. It was hard and freely movable. A friction rub was not heard over it. There was no ascites. The pelvic examination was negative. There was a marked secondary anemia with 5000 leukocytes. The blood Wassermann reaction was positive. She had come with the diagnosis of splenic anemia and wished an opinion as to the wisdom of operation for removal of the spleen, having been advised that nothing else offered any chance of helping her. In view of the marked secondary anemia and the diagnosis of syphilis of the liver and spleen, operation was advised against and specific treatment begun. Within a month she had gained 10 pounds and looked very much better. The liver had decreased in size and the edge of the spleen was 5 cm. from the navel. She noted that the spleen was reduced in size one week after treatment was begun. Three months after treatment was begun she had gained 30 pounds and felt greatly better. The edge of the liver was at the costal margin and the spleen was much smaller, although still readily palpable. A month later she had a normal period. Two years later she was seen and found to be in good general condition except for overweight. The periods had continued to be regular. The spleen was still somewhat enlarged but gave her no trouble and she regarded herself as perfectly well.

Liver. The changes in this organ are most important especially in diagnosis.

1. *Late Congenital Syphilis.* These cases show considerable similarity, and it is better to discuss them apart from the acquired cases. There are 5 cases in the series, the ages being three, thirteen, sixteen, eighteen and nineteen years. In all the cases there was evidence of syphilis in one or both parents. In all these cases the liver showed much the same condition. It was much enlarged generally and showed a remarkable, large, rounded, smooth mass or masses in the epigastrium, which caused distinct prominences (Fig. 2). In 2 of these patients there was in addition a small nodular mass felt on the right lobe. The spleen was much enlarged in 4 and the area of dullness increased in the other. All 5 patients had fever and ascites was present in 4 of them. It is not safe to draw

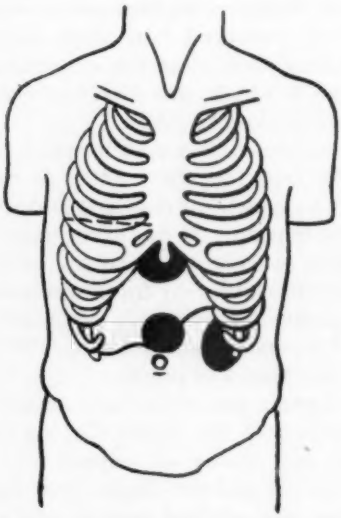

FIG. 2.—Large rounded prominence in late congenital syphilis. Enlargement of spleen.

conclusions from such a small number of cases but the comparatively uniform character of the liver tumor is suggestive.

The diagnosis in this group had not been made previously in any case. Abscess, new growth and hydatid cyst had been suspected. In general it may be said that the enlargement of the liver showed a less rapid response to treatment than in the acquired cases.

2. *Acquired Cases.* In the study of the tumor one point is worthy of special emphasis, and that is the relatively greater involvement of the left lobe as compared with the right in many of the cases. In 95 cases (5 others being congenital) the liver was enlarged or showed a tumor mass in 89, and in 49 of these the involvement of the left lobe was strikingly marked in comparison with the right.

This is an important point in diagnosis. In the previous paper a division was made into three groups, depending on the character of the change in the liver. This classification has worked well and there is no reason to change it. Some cases may show features of two groups but usually one form of change predominates.

(*a*) With general enlargement but no marked gross irregularity of the surface (43 cases). In some cases the liver was slightly irregular.

(*b*) With definite nodules (29 cases).

(*c*) Showing a marked prominence which might be described as a boss, sometimes associated with nodules elsewhere, but the large smooth enlargement being the striking feature (16 cases).

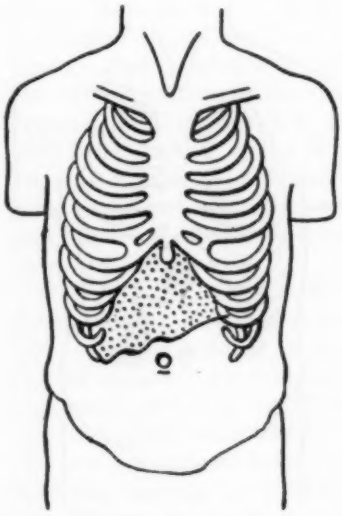

FIG. 3.—General enlargement of the liver, the surface having a slight irregular character.

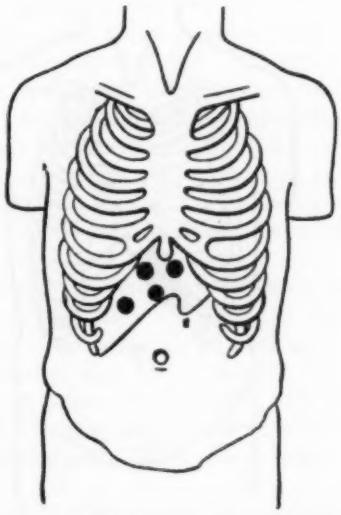

FIG. 4.—Nodules on the surface of the liver.

(*a*) *General Enlargement.* The extent of this varied from an edge which was 2 inches below the costal margin to cases in which the edge was below the navel. The surface was smooth and the liver hard in the majority; in 4 cases the surface was slightly irregular (Fig. 3). In 19 cases there was complaint of pain and tenderness on palpation, in some so severe that thorough palpation was impossible on account of the rigidity. The spleen was enlarged in 27 cases and in 15 cases ascites was present. There was marked distention of the surface veins in 10 cases. Fever occurred in 29 cases. It is easy to see that portal cirrhosis with enlargement or biliary cirrhosis might be suggested in the cases of this group. If there is myocardial insufficiency the enlarged liver may be regarded as due

to passive congestion. In the earlier series the incorrect diagnoses were: One was thought for a time to be hepatic abscess on account of fever, chills and sweats, but the condition was recognized later; 2 had cerebral lues which dominated the picture, and 2 had severe cardiac disease, to which the enlargement of the liver was ascribed.

(*b*) *Nodules.* In the majority these were particularly evident in the epigastrium or in the adjoining part of the right hypochondrium (18 cases) (Fig. 4). In 6 they were more or less general over the surface of the liver and in 4 there was a very large irregular nodular mass. Ascites was present in 13 cases. The spleen was enlarged in 17 cases. Prominence of the surface veins was marked in 9 cases. Fever occurred in 15 cases. The relatively greater involvement of the left lobe was marked in many of the cases of this group. The error in diagnosis most to be expected in this group is to regard the nodules as representing neoplasm. Tuberculous peritonitis had been diagnosed in 1 patient with ascites, the nodular liver being regarded as a thickened omentum.

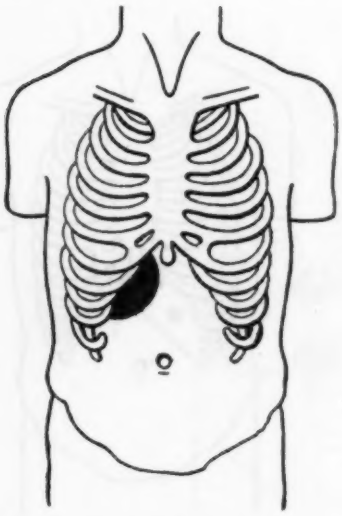

FIG. 5.—Large rounded mass projecting below the right costal margin.

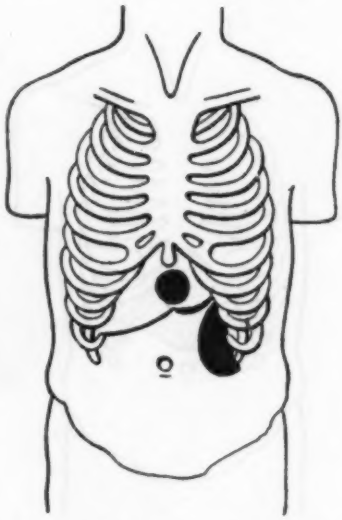

FIG. 6.—Large tumor with a rounded prominence. Marked enlargement of the spleen.

(*c*) *Rounded Tumor.* The size was enormous in some cases (Figs. 5 and 6), there being a large rounded projection which filled the whole upper abdomen. In several instances the enlargement of the spleen was remarkable; in 3 cases the organs practically touched and filled the whole of the upper abdomen. Ascites was present in 8 and the spleen was enlarged in 9 cases. In 1 a friction rub was heard over the mass. Fever was present in 13 cases. In the

earlier series only one error in diagnosis was made, the enlargement being regarded as due to malignant disease, but survival for two years and the appearance of a luetic skin eruption (rupia) gave the correct diagnosis.

Friction Rub. This was in mind particularly in the examination of the later cases of the series. Considerable emphasis was laid on its occurrence in the earlier literature and it was rather disappointing that it was found so rarely.

Diagnosis. As always, the most important point is some knowledge of the condition and its manifestations. The lack of recognition of the frequency of hepatic syphilis is an important factor in wrong diagnosis. The common error is to regard syphilis of the liver as another disease. In the great majority of cases the liver is altered in some way. With marked ascites it may be difficult or impossible to feel the liver but if an examination is made immediately after tapping it is usually possible to palpate it. The greatest difficulty arises in the cases seen late, when the liver has contracted. If it is possible to palpate it the usual marked irregularity may be suggestive. The Wassermann test is important if positive, but as a considerable number of the cases do not give a reaction, no great weight should be given to a negative report. The Wassermann reaction should be tried in the ascitic fluid in every doubtful case with ascites.

Difficulty may arise in several ways: (1) Some other disease is present which overshadows the hepatic disease, especially if the liver is not very large or the surface is smooth. Advanced myocardial degeneration with decompensation may give difficulty, the enlarged liver being regarded as due to passive congestion. There may be syphilis elsewhere, as in the nervous system or aorta, which attracts greater attention and is recognized. Extensive tuberculosis may dominate the picture.

2. Disease of the liver is recognized but its nature is not diagnosed. This is apparently the most frequent error and was due in some cases to the occurrence of fever and chills. These were regarded as being due to abscess of the liver, cholecystitis or cholangitis. Neoplasm, cirrhosis of various kinds, cholecystitis and cholangitis were diagnoses which had been made.

3. Abdominal disease is recognized but not the exact nature. Tuberculous peritonitis, carcinoma of the peritoneum and splenic anemia are examples.

General Features in Diagnosis. There may be a marked change in the general condition. The patient usually has lost weight and strength, is somewhat anemic, may have had hematemesis and suffered from abdominal pain. Naturally the possibility of malignant disease is suggested. The occurrence of fever suggests an infection. In the cases without any enlargement or evident change in the liver (6 in this series) only the knowledge of the possibility

of syphilis of the liver, the search for proof of infection (especially the Wassermann test) and the results of specific treatment could give the diagnosis. The necessity of keeping syphilis in mind as the cause of more or less continued fever is evident. With advanced cardiac or renal disease, tuberculosis, etc., dominating the picture and no special hepatic features being present, the diagnosis is not likely to be made.

Recognition of the Liver Condition. Several conditions have to be considered, especially the diagnosis (*a*) from cirrhosis, which is most likely to occur in the cases of uniform enlargement, and (*b*) from new growth, either of the liver, or in some cases, in which there is a single nodule, of the stomach or bowel; this is most likely in cases with marked nodular changes in the liver. (*c*) In the cases with the large, smooth, domelike tumor, abscess or cyst may be considered. (*d*) Ascites may give difficulty, and it is very important to palpate the abdomen immediately after tapping; it may be possible only then to feel an enlarged liver or a small nodule. Of less importance are (*e*) amyloid disease, (*f*) cholelithiasis, (*g*) splenic anemia and (*h*) Hodgkin's disease. There are some points which deserve emphasis. One is a history of previous tapping followed by improvement for a time. Another is the finding of relatively marked involvement of the left lobe as compared with the right. This, with any striking irregularity in the organ, should always suggest the possibility of syphilis. The enlargement of the spleen is important, but of course occurs in other hepatic conditions.

Features of the Tumor. (*a*) *General Enlargement of the Liver.* This is difficult to distinguish from portal cirrhosis with enlargement of fatty liver, especially as many of the patients give an alcoholic history. Careful examination should be made for any nodular enlargement, and this is particularly important immediately after tapping if there is ascites. In several cases a small nodular mass was felt coming from below the costal margin on deep inspiration, sometimes high up in the costal angle. The liver itself often feels very hard and the surface may be uneven and somewhat rough. Tenderness is sometimes quite marked. It is evident that the distinction from an ordinary cirrhosis is not easy. The knowledge of the possibility of syphilis is perhaps the greatest aid, as it suggests the Wassermann reaction and the therapeutic test. The value of this last is great and there need never be any hesitation in doing it, as no harm will result if the condition is not syphilitic.

(*b*) *Nodular Masses.* The diagnosis in this group may be very difficult and a nodule in the liver, particularly in the left lobe, may suggest malignant disease in the stomach or bowel or in the liver itself. The masses on the liver may be regarded as evidence of malignant disease, a mistake which it is easy to make if the general features are marked. The following is such a case: A white

woman, aged thirty-one years, came complaining of pain in the upper left epigastrium and the statement that a diagnosis of carcinoma of the stomach had been made. She had been married for twelve years and had one child; there was no history of miscarriages. Her illness began five months before with pain near the left costal margin. The first diagnosis made was pleurisy. She entered one hospital and was treated for "stomach trouble." In a second hospital a diagnosis of tuberculosis of the left kidney was made. (It is interesting that we found a stricture of the ureter but on the right side.) In a third hospital attention was particularly directed to the kidney but nothing was found. The next diagnosis was cancer of the stomach with which she came to us. She was emaciated, having lost 20 pounds, showed jaundice and had a distinct prominence below the upper part of the left costal margin; this was very tender. The right lobe of the liver was slightly enlarged, the left quite markedly so and on it was one nodule. The spleen was not felt but the dullness was increased. She had fever varying from 101° to 102° F. The Wassermann reaction was strongly positive. She was given mercury and iodide; the fever disappeared in forty-eight hours and the pain and tenderness in a week. She gained rapidly in weight. She has done very well and ten years later is in excellent health.

(*c*) *Rounded Tumors.* In patients with this condition the common mistake is to consider the mass as new growth, and in some cases in which this diagnosis was made it was only the passage of time which raised doubt of this diagnosis being correct. In certain other cases of the earlier series the liver had been punctured a number of times with the expectation of obtaining pus. Unless there is knowledge of syphilis causing such a tumor the diagnosis is hardly likely to be made.

Secondary Cirrhosis. We know from autopsy experience that in a certain number of the cases of hepatic syphilis marked contraction occurs, which in some cases advances to an extreme grade, as seen in the botyroid liver. How rapidly this occurs we have not had much opportunity of observing. The cases which have given the greatest difficulty in diagnosis have been some in which the liver was becoming smaller, somewhat hard and possibly was not particularly irregular. Here the difficulty was in distinguishing syphilis from portal cirrhosis. As many of the patients are heavy drinkers, it is probable that portal cirrhosis plays a part in the contraction. A very careful history may throw light on the problem if there is a definite note of previous ascites which has disappeared or lessened, or that the liver formerly was a great deal larger. Suspicion may be aroused and if the Wassermann reaction is positive this is additional evidence. In some of these patients the results under mercury and iodide have been so striking that they have been very helpful in coming to an exact diagnosis. If there is quite marked

enlargement of the spleen the decrease in size in this under treatment is often about as striking as the change in the patients with marked enlargement of the liver.

Wassermann Reaction. As this is negative in a considerable proportion of cases, no importance whatsoever should be given to a negative result, if the clinical features are suggestive. The importance of always having the Wassermann reaction tried with ascitic fluid should be remembered.

Therapeutic Test. There is always some risk of error in trusting to the result of therapy to make a diagnosis, but in this condition the results are so striking that it has to be included as a method of diagnosis. We have both the general effect, shown particularly on the fever, and the local changes in the liver. The effect on the fever is usually very striking, in many cases the temperature falling to normal within forty-eight hours. The influence on the liver itself is almost equally marked; two or three weeks may show a marked decrease in the size of the liver as a whole or of prominences on its surface. In some cases the spleen also shows a remarkably rapid decrease in size. Sometimes the enlarged liver in portal cirrhosis may show a rapid decrease in size, but this is not likely to cause confusion. Ascites, if present, usually lessens rapidly.

Course. Judging from autopsy experience, recovery must be comparatively common. So far as we can decide, the hepatic functions are completely restored, as in many patients dying of other diseases and having extensive changes in the liver from syphilis there is no evidence of any hepatic disturbance. It is just as certain that a certain number die of the disease and the majority of these unrecognized. In cases with extensive cirrhotic changes the outlook is practically the same as in ordinary cirrhosis. In such cases we must not expect to do much by specific treatment.

There were 24 deaths among this series of 100 cases. Of these, in only 1 was death due directly and immediately to hepatic syphilis. In this case the process caused obliteration of the hepatic veins and inferior vena cava with resulting thrombosis. In 9 cases death resulted indirectly, in 7 from resulting cirrhosis, in 1 from hemorrhage from esophageal varices and in 1 from amyloid disease. Some of the patients with cirrhosis had received active treatment with resulting temporary improvement. In 1 case death resulted from carcinoma of the peritoneum, in 1 from chronic nephritis and uremia, in 1 from pulmonary tuberculosis, in 2 from cerebral syphilis, in 1 from acute leukemia and in 1 from pernicious anemia. In the other patients improvement was the rule as regards the liver condition but death resulted from cardiac disease.

In general, it may be said that the patients with syphilis of the liver alone, whose condition otherwise is comparatively good, do extremely well if properly and promptly treated. The improvement is usually very marked and the subsequent course has not shown

a return of the condition in any patient so far as we have been able to discover. Some patients have now been followed for twenty-five years and remain in perfectly good health.

Treatment. This is the usual therapy for syphilis with mercury and iodide, placing special emphasis on the administration of iodide of sodium or potassium. In many of the cases iodide alone was given with a perfect result as regards the relief of symptoms. No difference could be observed when mercury was added, but it is wise to give both drugs. Dramatic results, such as almost immediate disappearance of the fever, reduction in the size of the liver and rapid gain in the general state and weight were seen when iodide alone was given. One patient gained 25 pounds in a month.

We must recognize that in some cases while we can influence the syphilitic process in the liver, we cannot prevent or materially affect resulting or coincident cirrhosis unless the cases are seen early and recognized.

Arsenic Preparations. There is only one statement to be made with regard to these, and that is they are absolutely contraindicated in the great majority of cases. There is no possible excuse for administering arsphenamine or any other arsenic preparation to a patient who has syphilitic disease of the liver. The danger of causing acute damage to the liver, resulting in a condition of toxemia, is undoubtedly great. It is perfectly true that some patients take arsphenamine safely, but it is equally true that a certain number of patients are being killed each year as a result of this treatment. Nothing can be more satisfactory than the treatment by mercury and iodide in every patient that we have seen. It is possible that an occasional patient may not respond to these remedies, and it may be felt that an arsenic preparation should be given. In such a case this may be justified, but the dose should be very small, the patient watched carefully and careful studies of the liver function made. This treatment should be given only after most careful consideration. A certain number of patients with syphilis of the liver have been admitted in a very serious condition following the giving of arsphenamine. These are not included in the present series.

Splenectomy. In patients with unusual enlargement of the spleen in association with syphilis of the liver, splenectomy may be considered. No rule can be laid down and each patient should be carefully studied as a distinct problem. The spleen usually decreases rapidly in size under specific treatment, but may cause symptoms from its size and weight. A persistent anemia may follow. Splenectomy may then be advisable. In no case in this series did it seem indicated. The cases in the literature have been collected by Farley[1] in reporting a case.

[1] Bulletin of the Ayer Clinical Laboratory of the Pennsylvania Hospital, 1925, No. 9, p. 45.

Conclusions. 1. Syphilis of the liver presents a very varied clinical picture with prominent general symptoms in many cases, of which loss in weight is marked. The duration of the symptoms may be prolonged and there may be periods of improvement. Fever is a common occurrence.

2. There are features suggestive of hepatic disease in the majority of the cases. Enlargement or tumor is common. This may suggest other conditions, especially malignant disease. A striking feature is the relatively marked enlargement of the left lobe as compared with the right.

3. The diagnosis may be obscured by other disease conditions or the liver condition may be interpreted wrongly. Knowledge of the features of hepatic syphilis and the therapeutic test are important aids.

4. Specific treatment can influence the syphilitic process, but not its results (cirrhosis, amyloid).

PANCREATIC TUMORS, MALIGNANT AND BENIGN.*

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(From the Lenox Hill Hospital, New York City.)

Notwithstanding the great advances made within recent years in the field of internal medicine, the diseases of the pancreas still offer many difficulties for diagnosis. The reason for this is the almost hidden position of this organ and its great ability to continue its function when a portion of it is still intact.

Of the large class of pancreatic affections we select for this paper the discussion of tumors of the pancreas, malignant and benign.

In his excellent book, *Pancréatites chroniques avec ictère*, which embraces pancreatic tumors with jaundice, Mallet-Guy[1] comes to the following conclusions:

1. Under the anatomic expression "chronic pancreatitis" various clinical entities have been described, among which there is one requiring surgery characterized by chronic jaundice and inflammation of the pancreas.

2. The choledochus is merely compressed by an inflammatory tumor. When the latter is dissipated the canal becomes patent.

3. The pancreatic lesion consists of an interstitial inflammation not involving the glandular parenchyma to any extent and causing therefore but trivial disturbances of function.

* Read before the Nassau County Medical Society, April 27, 1926, at Garden City, L. I., N. Y.

4. Two causes of this trouble are well known—chronic cholecystitis carrying infection through the lymphatics and syphilis, the latter occasionally when histologically examined simulating a neoplasm.

5. Attacks of pain in the epigastrium and lumbar region, loss in weight and jaundice are usually the symptoms encountered. A correct clinical diagnosis is impossible and the assumption of a calculus in the choledochus is usually made. The surgical exploration shows that there is no stone nor an organic lesion at the papilla of Vater, but a thickening of the pancreas, which appears to be malignant. These findings are chracteristic and sometimes it is possible to make the correct diagnosis of a chronic pancreatitis.

6. The treatment consists in biliary drainage (surgical) which relieves the tension in the choledochus and cures the pancreatitis.

7. Cholecystgastrostomy shows the best results.

8. A plain cholecystostomy or Kehr's choledochostomy are also occasionally used with benefit.

9. In the absence of an examination by biopsy, the surgical diagnosis of chronic pancreatitis with icterus must be confirmed by one of the following criteria:

(*a*) Cure resulting and bile ceasing to flow from the new outlet.

(*b*) Continuation of the cure after the closure of the cholecystostomy.

(*c*) The cure lasting one and a half years after the establishment of the anastomosis.

(*d*) Demonstration of the dissipation of the tumor and especially of the nonfunctioning of the anastomotic opening.

In the last two years I had in my private practice 9 cases of pancreatic tumors without and with icterus in which a diagnosis could be made clinically or in the course of an operation. I thought it would be of interest to briefly describe these cases and then make a few remarks regarding them.

We may divide the cases of pancreatic tumor as follows:

(*a*) Those of a malignant type, without icterus.

(*b*) Those of an indefinite type, without icterus.

(*c*) Those of a benign type, with icterus.

(*d*) Those of an indefinite character, with icterus.

GROUP A. TUMORS OF THE PANCREAS OF A MALIGNANT TYPE WITHOUT ICTERUS.

Case Reports. CASE I.—V. R., aged sixty-two years, had his first attack of pain in the upper right quadrant three years before examination in October, 1924. The attacks gradually increased in severity and frequency. The pain radiated to the back. The patient was more comfortable when sitting or standing than in the recumbent posture. Hence he was compelled to sleep in a chair most of the time.

The physical examination revealed tenderness in the epigastrium and a liver that was enlarged to three fingers below the right costal margin.

The gastric contents were: HCl, 50; acidity, 85; blood, negative. The

bile was like pea soup in appearance and acid in reaction, but contained no free HCl. There was no color reaction after the instillation of a 5 per cent peptone solution into the duodenum. The pancreatic ferments were: Amylopsin, 0; steapsin, 0; trypsin, 0. Another examination of the bile on October 12 revealed the following: The duodenal contents were light yellow and turbid; alkaline; numerous blackish particles were present. Microscopically, pus corpuscles, mucus and cholesterin crystals were found. The ferments were: Amylopsin, 2; steapsin, 2; trypsin, 1. The Wassermann reaction was negative. The digestive test capsule was recovered after twenty-three hours; two-thirds of the potato and part of the meat and thymus were present; everything else and the nuclei had disappeared.

The patient was operated upon October 15, 1924. The pancreas was infiltrated throughout, well palpated in its course across the spine; in one place it was distinctly nodular. The diagnosis of chronic pancreatitis with malignancy was made. The gall bladder was firmly adherent to the surrounding tissues and omentum. A cholecystogastrostomy was performed.

The patient felt slightly relieved for a week or so after the operation. Thereafter the pains reappeared and persisted with great severity, even under opiates. Nutrition became more difficult and patient gradually succumbed after four to five months.

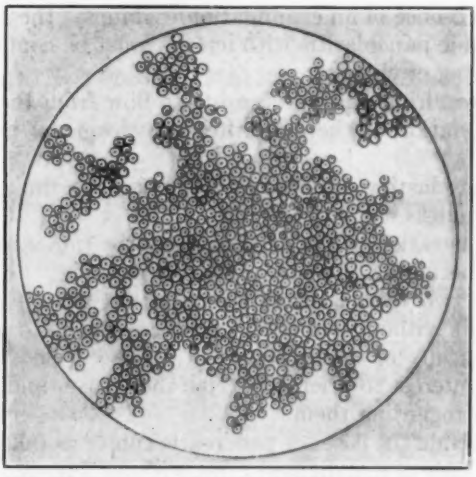

FIG. 1.—The stool, on November 9, 1923, after bead test showed microscopically that all the nuclei were present.

CASE II.—I. S., aged fifty years, two years before examination, November 5, 1923, had a hemorrhage from the stomach and intestine. Since then he was occasionally troubled with indigestion. For the last two months he had complained of pain right after meals in the gastric region, lasting two hours. The pain lately had become more permanent in the left part of the stomach, lasting the whole day and part of the night. The patient did not vomit. He lost 20 pounds in one year. The stools were hard and formed and occasionally black. There was anorexia and ructus present. A resistance was felt in the right hypochondrium.

The gastric contents were: HCl, 0; Ac, 0; neutral; rennet, 0; blood +, trace; Boas-Oppler bacilli present. The string did not show any blood or bile stain. The length of the string was 65 cm. The stool was positive for blood. The Roentgen ray examination revealed a persistent defect

involving the entire stomach; the first portion of the duodenum was dilated and deformed. The blood count was as follows: Hemoglobin, 55 per cent; red blood cells, 4,450,000; white blood cells, 7200; polymorphonuclears, 80 per cent. The digestive test capsule was recovered after twenty hours; there remained potato, whole; trace of meat; thymus, whole, and nuclei present (Fig. 1).

A diagnosis of cancer of the pancreas involving secondarily stomach and liver was made. A well-regulated diet and the constant use of nerve sedatives and opiates made the patient's sufferings lighter and probably prolonged life somewhat. After a period of about four to six months the patient succumbed.

CASE III.—Mrs. C. B., aged forty years, in 1910 had an injury (?) to her stomach from a fall. About eleven weeks before examination, July 8, 1925, the patient had a severe fright. Since that time she has had complete loss of appetite and pain and gas in the stomach, with belching. She occasionally had nausea and vomiting. The patient never vomited food from the day before. She lost 20 pounds in two months, and complained of increasing weakness.

Physical examination revealed a resistance palpable under the left costal margin.

The blood count was as follows: Hemoglobin, 60 per cent; red blood cells, 4,000,000; white blood cells, 10,000; polymorphonuclears, 70 per cent. The string test showed no blood stain; bile was present from 55 cm. to the end. The stool showed that blood was present. The gastric contents were: Free HCl, 0; Ac, 30; blood, present; rennet, 0; the contents had a putrid odor. The urine contained albumin but no sugar.

The patient was operated upon by Dr. F. Torek on July 15, 1925. The findings were as follows: The cardiac portion of the stomach was densely infiltrated, the lesser omentum likewise; the stomach was firmly attached to the diaphragm. The pancreas was infiltrated. A radical operation was impossible. The patient died, August 2, from symptoms of intestinal obstruction.

CASE IV.—B. G. L., aged fifty-six years, for the last six months (January 1, 1926) had been complaining of ructus, loss of appetite and for four months he had pains on the left side of back (gastric region and lower down), principally in the recumbent posture. He would not lie on his left side or back; he was comfortable when lying on right side. He was awakened every hour during the night with these pains. He felt better when sitting or standing. He lost 30 pounds in four months and felt quite weak. He was always constipated, but more so recently.

The physical examination revealed that the liver was somewhat enlarged; there was occasional stiffening of the stomach.

The blood count was as follows: Hemoglobin, 73 per cent; red blood cells, 4,580,000; white blood cells, 8100; polymorphonuclears, 86 per cent. The Roentgen ray examination did not reveal any defects in the stomach or duodenum but a slight gastric retention.

The string test was performed on January 4, 1926, and showed a bile stain 60 cm. from the lips to the end of the string but no blood stain. The feces were negative for blood. The gastric contents were dark brown and contained HCl, 5, in the fasting specimen. The contents after a test meal were: HCl, 14; Ac, 28; blood positive. The bile was fairly clear and alkaline. The pancreatic ferments were amylopsin, 6; steapsin, 0; trypsin, 0.

A diagnosis of pancreatic tumor, probably malignant, was made and an operation advised. Dr. Brewer performed the operation at the Presbyterian Hospital. A tumor of the body of the pancreas was found and

secondary deposits in the liver. The latter showed a characteristic carcinoma. The abdomen was closed. The patient succumbed 2 or 3 months afterward.

GROUP B. TUMORS OF THE PANCREAS OF AN INDEFINITE TYPE WITHOUT ICTERUS.

CASE V.—B. C., aged about fifty years, had several attacks of severe upper abdominal pains of a few hours' duration within a period of ten months. For the last four months he had complained of gastric distress right after meals, lasting one to two hours. He lost 15 pounds in weight and was extremely constipated.

The physical examination revealed a dilatation of the stomach, extending a hand's width below the navel. The liver was swollen, overlapping the right costal margin by two to three fingers' width. Epigastrium and gall bladder region were painful to pressure.

The string test was as follows: Blood stain, 16 to 19 inches; bile stain, 21 inches to the end of the string. The gastric contents were: HCl, 20; Ac, 60; mucus present but no blood. The digestive test capsule was recovered after thirty-two hours; there remained thymus but no nuclei. The blood count was: Hemoglobin, 80 per cent; white blood cells, 6400; polymorphonuclears, 46 per cent.

A diagnosis of gastric ulcer and probable gall bladder trouble was made and duodenal alimentation decided upon. The tube did not enter the duodenum in five days. The tube with bead attachment passed the pylorus in two days and duodenal alimentation instituted. The patient was free from discomfort for two weeks.

The bile examination on June 20, 1924, revealed dark yellow and turbid, brownish, bunch-berry particles and crystals were present. The pancreatic ferments were amylopsin, 6; steapsin, 3; trypsin, 2.

On July 3, 1924, the bile was dark yellow and turbid. Brownish-looking crystals were present. The ferments were amylopsin, 6; steapsin, 2; trypsin, 1.

After removing the tube the string test showed a bile stain 65 cm. to the end but no blood stain, indicating a probable healing of the ulcer.

The Roentgen ray examination revealed the following: Duodenum, small and tucked in behind the prepyloric region; suspicious for gall bladder disease.

When food by mouth was resumed the gastric distress reappeared in two or three days and remained stationary even after the lightest foods. Soon afterward the patient had a very severe attack of abdominal pain necessitating a hypodermic of morphin. An exploratory laparotomy was then advised. The operation revealed a tumor of the pancreas but no stone.

GROUP C. TUMORS OF THE PANCREAS OF A BENIGN TYPE, WITH JAUNDICE.

CASE VI.—M. H., aged sixty years, had had attacks of pain on and off for ten years. Lately he has been jaundiced. He does not complain of itching.

Physical examination reveals tenderness in the hepatic region.

On January 18, 1924, the gastric contents were: HCl, 0; Ac, 50. The urine contained abundant biliary pigment. On January 22, 1924, the gastric contents were: HCl, 4; Ac, 36; no blood. There was no blood in the feces. On January 26, 1924, the bile was examined and revealed it yellow-brown and turbid; few cholesterin crystals and mucus were present. The ferments were amylopsin, 3; steapsin, 0; trypsin, 0. The string test examined on January 23, 1924, showed the presence of a bile stain from 60 cm. to the end.

The Roentgen ray examination revealed "possibly chronic cholecystitis."

A diagnosis of a tumor of the pancreas was tentatively made, and an operation advised. This was performed by Dr. Willy Meyer. The findings were as follows: The gall bladder was of medium size; the liver border was covered with firmly adherent omentum down to the cystic duct which was greatly distended in the shape of an S Romanum. The head of the pancreas was enlarged and infiltrated but not nodular. The stomach and liver were not involved. A frozen section taken from the head of the pancreas was at first reported as a "lymphosarcoma," but this diagnosis was later revoked. A cholecystogastrostomy was performed.

On February 20, 1924, the duodenal contents were light green and very turbid. There was a trace of color reaction. Cholesterin, bunch-berry and brownish-looking crystals, as well as brownish particles, were present. The ferments were amylopsin, 1; steapsin, 1; trypsin, 1.

On March 4, 1926, the patient felt well all along and did not require any medical aid.

Case VII.*—A. M., aged seventy-seven years, was troubled with biliary colic for many years and lately developed persistent jaundice. The liver was found slightly enlarged. The urine contained biliary pigment. The digestive test capsule showed after thirty-six hours that potato and thymus with few nuclei were present.

On December 19, 1924, the bile was dark yellow and turbid. There were numerous blackish particles present, some stony hard. After peptone there was a trace of color reaction. The ferments were amylopsin, 3; steapsin, 1; trypsin, 2. On December 24 the bile was yellowish and turbid. The ferments were amylopsin, 3; steapsin, 1; trypsin, 2. After an oil instillation there was no color reaction. There were some pus cells, calcium bilirubin and cholesterin crystals present. On November 23, the bile was dark brown and very turbid. The ferments were amylopsin, 5; steapsin, 1; trypsin, 1. There was no color reaction after the instillation of 25 per cent glucose.

The Graham test with tetraïodophenolphthalein by the tube failed to give any gall-bladder shadow. The diagnosis fluctuated between gall stones and a tumor of the pancreas. An operation by Dr. Edward Ill on September 26, 1924, revealed a tumor of the head of the pancreas compressing the choledochus; the gall bladder was completely destroyed and its vestiges imbedded in adhesions. A tube was inserted in what previously had been a gall bladder, and biliary drainage effected. The jaundice has cleared up quickly and the patient enjoyed good health ever since. He is now seventy-nine years of age and feeling perfectly well.

Group D. Chronic Pancreatitis of Doubtful Type with Jaundice.

Case VIII†.—J. G., aged fifty-six years, has had gastric distress for three months with loss of appetite. He has been jaundiced for the last six weeks, but did not complain of any severe colicky pain in the upper abdomen. There was no rise in temperature. The patient had lost a great deal of weight.

The Wassermann reaction was 2+. The gastric contents were: HCl, +; Ac, 105; no blood. The sting test showed a trace of bile at the end but no blood stain. The duodenal contents were light yellow; neutral in reaction; cholesterin and bunch-berry crystals were present as well as

* As this case was fully described in my paper "A Few Instances of Nature's Cure of Gall-stone Disease," I shall give but a few details here.

† This case has been described in detail in my paper, Additional Remarks on Cholecystography (Med. J. and Rec., 1926, **123**, 40), therefore but a short résumé is here given.

big conglomerations of cholesterin crystals. There were also a few pus corpuscles and epithelial cells. The ferments were amylopsin, 3; steapsin, 1; trypsin, 1. The Graham test showed no gall bladder shadow.

The diagnosis fluctuated between carcinoma and a benign tumor or gumma of the pancreas. Dr. F. Torek performed the operation. The gall bladder was found to be three-quarters the size of a man's fist, intensely filled with a dark, black, tarry bile. The pancreas was hard and nodular; no stones were palpated in the common bile duct. The cause of the obstruction was the pancreas. A cholecystogastrostomy was done. The patient did well for a few days, when he was seized with pneumonia and succumbed.

CASE IX.—H. B., aged thirty-five years, had a severe attack of biliary colic with jaundice about fifteen years ago. For six weeks before examination, January 2, 1926, the patient has been jaundiced. At the onset he had pain in the epigastrium which disappeared after bicarbonate of soda. His appetite was poor. He complained of increasing weakness and itching. The stools were clay colored.

The gastric contents were: HCl, 38; Ac, 78. The string test was performed on January 4, 1926, and showed the following: Blood stain, 49 to 51 cm.; trace of bile, 56 cm. to end. The digestive test capsule was recovered after forty hours. Everything had disappeared. The urine contained biliary pigment and no urobilinogen.

The duodenal contents were examined on January 7, 1926, and were grayish and turbid; acid in reaction, but no free HCl. The ferments were amylopsin, 6; steapsin, 2; trypsin, 0. There was no color reaction after the instillation of 5 per cent peptone, but all the specimens contained a trace of bile; all alkaline. The total time was forty minutes and the total quantity was 20 cc. There were few red and few white blood cells; mucus. The diagnosis fluctuated between gall stones and a pancreatic tumor. An operation was advised and it was performed by Dr. John F. Erdman. After a preparatory transfusion which brought down the coagulation time to eight minutes the patient was operated upon the same day. His gall bladder was found distended—a typical Courvoisier; it was anastomosed to the stomach. A large area of infiltration was found at the head of the pancreas which Dr. Erdman believed to be malignant. The patient did well for about twenty-four hours, when he suddenly collapsed and died within a short time with no assigned reason, there having been no hemorrhage or peritonitis. Dr. Erdman ascribed the death to probable dysfunction of the liver.

The question whether the tumor of the pancreas was malignant or benign cannot be decided. The clinical symptoms and objective findings are compatible alike, with a malignant and a benign pancreatitis.

Discussion. In reviewing the cases just described the following is noteworthy: In most of the patients the principal symptoms were loss of appetite (in some disgust for food) and more or less constant distress in the epigastric region with frequent eructations of gas. Severe attacks of pain, especially in the left hypochondrium, radiating to the dorsal vertebra were met with. In a few of the patients the pain was more pronounced in the recumbent position, while relief was obtained either in standing, sitting or lying on the right side.

In the malignant cases there is a gradual progression of the disease without any marked periods of intermission.

In the benign variety of chronic pancreatitis there are periods of

suffering alternating with more or less prolonged intervals of euphoria. The bead test shows often, especially in the malignant cases, a return of many substances undigested, especially the nuclei (see I. S.). In some, however, we found a complete disappearance of the nuclei.

The pancreatic juice almost always reveals a diminished activity and sometimes a complete lack of some of the ferments (this refers to a greater extent to the malignant conditions of the pancreas, especially when the malady is already advanced). The bile is usually turbid, containing cholesterin crystals and often pus corpuscles. The gastric contents frequently shows achylia or a high degree of subacidity in the malignant cases and hyperchlorhydria or euchlorhydria in the benign type.

Jaundice is encountered in a number of these cases, principally when the head of the pancreas is especially involved. The diagnosis is then somewhat facilitated. In all the cases above detailed there was a chronic cholecystitis present. This, however, did not impress one as the main lesion, excepting in cases accompanied with jaundice. A pancreatic affection presented itself as a possibility and upon further investigation (lack or diminution of the trypsin ferment) as a probability.

On account of the possibility of malignancy on one hand and a good therapeutic effect by an operation on the other hand, surgical intervention is frequently practised in these cases. The exploration at the laparotomy sometimes helps to make a differential diagnosis. It certainly clears the field for further procedures. Thus, in chronic cholecystitis with or without stones but without any involvement of the pancreas a cholecystectomy will be done. When the pancreas is found enlarged and hardened, which may be due to an inflammation or a neoplasm, the gall bladder is usually not removed and a drainage operation for the gall bladder, either into the stomach, duodenum or outside the skin, is done. This operation can effect a cure in the benign conditions and bring much alleviation in the malignant states. If secondary deposits of a neoplasm are found involving vital organs (liver, etc.), and no distinct benefit expected from any further procedures, then the abdomen is closed with the only satisfaction of a correct diagnosis and the knowledge that everything possible had been done for the patient.

The two cases of pancreatic tumors (due to simple inflammation) causing jaundice, with perfect recovery, one after simple biliary drainage and the other after cholecystogastrostomy, deserve special mention. In both the existing condition was very serious. It simulated a malignant disease of the gall bladder or pancreas. If no operation would have been done they would certainly have succumbed after great suffering. The simple operation of biliary drainage relieved the pancreas and in a short time both patients

recovered and remained well up to date (about two years), with a good outlook for a future happy life.

The lesson to be learned from these cases is, not to give in easily to the diagnosis of a malignant neoplasm of the pancreas or gall bladder and say "hands off, we cannot accomplish anything." If there is a possibility of doubt, we should take the chances and have the patient, provided he is not too far gone, operated upon.

By acting according to this precept we will frequently save some patient's life by the boons of surgery.

Conclusions. 1. Pain in the left side of the back corresponding to the gastric region, more pronounced when lying, and relieved in the sitting posture, is frequently encountered in pancreatic disease (especially when malignant).

2. Diminished activity of the pancreatic ferments combined with absence of the trypsin ferment is an indication of a pancreatic lesion (often malignant).

3. Jaundice due to compression of the choledochus by the head of the pancreas should always indicate operation, with establishment of drainage for the bile.

REFERENCE.

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NINETY TUMORS OF THE PAROTID REGION

In all of Which the Postoperative History was Traced.

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In 1904 Francis Carter Wood published an important paper, "The Mixed Tumors of the Salivary Glands," in which he not only gave the results of his careful study and analysis of 59 cases collected from the various hospitals of New York, but also reviewed and criticized the literature of the subject, and closed with an extensive bibliography.

In 1912 Louis B. Wilson and B. C. Willis published another paper, "The So-called Mixed Tumors of the Salivary Glands," in which was an analysis of 56 tumors removed at operations at St. Mary's Hospital (Mayo Clinic), from January, 1905 to April 10, 1911, and to which was also appended a bibliography of the subject embracing the interval between the appearance of Wood's paper and the preparation of their own.

A year later, 1913, H. Heineke wrote "Die Geschwülste der Speicheldrüsen," carefully reviewed the subject in all its aspects, and closed with 299 references to the literature bearing upon it.

In 1921 R. Kennon, in a paper "Tumors of the Salivary Glands with their After History," collected 124 cases from the Pathological Department of the Thompson Yates Laboratory and the Royal Infirmary of Liverpool, and traced the postoperative history in 38. Kennon's paper is entirely original and is without a bibliography.

Whoever, in the face of these excellent contributions, undertakes to add to the literature might well be called upon to apologize unless actuated by some definite motive, yet since 1913 at least 75 additional papers have appeared.

The greater the number of cases from which conclusions can be drawn and statistics computed, the greater the probability of the correctness of both. If to the 59 cases studied by Wood, and the 56 studied by Wilson and Willis, be added the 90 new cases herein to be reported, and the 154 cases collected from the literature, a total of 359 cases, probably the largest number ever assembled, becomes available for consideration.

The present research is founded upon the histological and clinical study of 90 cases, none of which has heretofore appeared in the literature. It was not originally intended to be a comprehensive study of mixed tumors: It was much more modest in scope and contemplated no more than an attempt to answer the following questions:

1. Does the varying histologic structure of mixed tumors regularly enough coincide with their subsequent clinical course to enable a reasonably accurate prognosis to be made after a microscopic examination?
2. Do mixed tumors frequently "become sarcomatous," as they are commonly supposed to do?
3. How frequently do they "become carcinomatous," as they are said to do?
4. Did those mixed tumors said to have "become sarcomatous" or to have undergone "carcinomatous degeneration" behave clinically as carcinomas and sarcomas ordinarily do?

But these problems soon proved to be much less simple than was at first supposed, and to answer them it became necessary to be in possession of all the information it was possible to obtain from every source available.

Above all things it became necessary to correlate the histologic appearances with the preoperative and postoperative histories of the patients operated upon, and to have the greatest possible number of cases whose operations were performed long enough ago to afford ample opportunity for recurrence and other late phenomena.

The 90 cases were operated upon in a number of hospitals in Philadelphia and one in Scranton, and thanks are now accorded to

Dr. John R. Paul, of the Pennsylvania Hospital, Dr. Stanley P. Reimann, of the Lankenau Hospital, Prof. Bowman C. Crowell, of the Jefferson College and Hospital, Dr. J. M. Wainwright, of the Moses Taylor Hospital of Scranton, Dr. C. Y. White, of the Episcopal Hospital, and to Prof. Eugene A. Case, of the Graduate School of Medicine of the University of Pennsylvania and the Medico-Chirurgical and Polyclinic Hospitals, for the assistance they rendered in searching out and making available such cases as had come under observation in their respective institutions.

The "follow up" of so many cases necessitated a considerable amount of correspondence, in which a number of the surgeons kindly assisted, and for that aid thankful recognition is here expressed. Thanks are extended also to Mr. E. M. Jameson, a senior student of medicine, who spent much precious time in collecting data and histories.

To have any considerable number of salivary gland tumors come under observation, both before and after operation, so that they may be studied both from the pathologic and clinical points of view, is a privilege enjoyed by very few. To obtain a large number, one is obliged to content himself with hospital records, preserved specimens and microscopic slides.

The material and data used in the preparation of this paper were mostly of that nature, and were in part above addition because of the length of time that had elapsed since the operations were performed, during which sometimes both patient and surgeon had died, the material been thrown away or the notes lost. Such circumstances result in unequal data. Thus, the number of cases whose age is known is not the same as that whose sex is known, and both differ from the number of which the side upon which the tumor occurred is known, and so on.

The case histories were frequently indefinite as to the localization of the tumors. Some were said to have been "of the parotid," some "in the parotid," some "in front of the parotid," some "behind the parotid," some "in front of the ear," some "behind the ear," some "at the angle of the jaw," some "in the neck below the jaw" and some "in the neck." It was not always possible to know whether a tumor had been in relation with a salivary gland or only adjacent to one.

This difficulty was overcome by adopting Wood's plan of regarding mixed tumors of the salivary glands and neck as belonging to the same class, and ignoring their precise localization.

If one were writing, as many have done, of tumors of the parotid or of tumors of the submaxillary glands the indefiniteness of the data might be embarrassing, but Tendenet long ago pointed out that the tumors under consideration are "*in* but not *of* the parotid gland," so it really makes little difference where they are said to be, provided, of course, that they are in the region concerned.

Wood even went so far as to admit to his collection of cases, mixed tumors of the lip, but none of them have been included in this research.

The varying positions in which the mixed tumors occur recalls the long controversy as to their histogenesis that made up so large a part of the literature, especially between the years 1895 and 1905.

The tumors in question were known to the early writers on pathology, but were confused with hypertrophies.

Virchow recognized them as tumors, but found them difficult to classify, and in "Die krankhaften Geschwülste" calls them "enchondromas" and "diffuse enchondromas."

The presence of other histologic components was early recognized, and the tumors were frequently spoken of as "zusammengesetzt," or compounded. Little by little they came to be called mixed tumors. All of the early German pathologists regarded them as derived from the connective tissues, and supposed any epithelial-like structures to be vestiges of the gland in which they occurred. French pathologists, on the other hand, seemed generally to incline to the thought that they were primarily epithelial and derived from the gland tissue proper.

Not many pathologists of the present day believe the tumors to develop from the tissue of the gland itself, but Fraser, by ligating the submaxillary ducts of dogs, produced lesions that he believed to be identical with mixed tumors, at least in their histological aspect.

In 1879 Wartmann expressed the opinion that the polyhedral cells, so frequent in their histologic structure, were derived from the lymphatic endothelium. This idea profoundly influenced Rudolph Volkmann, who, in 1895, wrote a long paper, "Ueber endotheliale Geschwülste zugleich Beitrag zu der Speicheldrüsen- und Gaumentumoren," in which he believed that he had proved the endothelial origin of the mixed tumors in general. He immediately obtained a large following, and case reports at once began to appear under the caption, "Endothelioma of the Parotid," and so on. Even in France the new idea was kindly received and was earnestly supported by Curtis and Phocas. It soon spread to all countries, and is still held by some contemporary pathologists.

In 1899 Hinsberg, after painstaking histologic study of 9 mixed tumors, wrote "Beiträge zur Entwickelungsgeschichte und Natur der Mundspeicheldrüsentumoren," in which he so adversely criticized the endothelial theory of their origin that the pendulum of opinion began to swing back to the earlier views. He was strongly supported by Borrmann* (Lubarsch and Ostertag's, *Ergebn. d. allg. Path. u. path. Anat.*, 1901, **7**, 807).

* As the references at the close of this article are arranged to give a survey of the whole subject, those references which, like the present one, have been included in one of the three comprehensive reviews are included in the text.

Krompecher studied a number of mixed tumors in 1908 (Zeigler's *Beitr.*, 1908, **44**, 51, 88), and finding that basal squamous epithelial cells were present, became convinced that mixed tumors were but varieties of his "Basalzellenkrebs." In this he seems to have been the victim of too great enthusiasm for his own particular theory.

The diverse theories of histogenesis were reflected in the conflicting nomenclature employed by pathologists. Writers, adhering to the glandular origin of the tumors, called them "epitheliomas:" those following Volkmann, endotheliomas; those uncertain of the origin, and thinking to see resemblances to familiar tumors, sometimes described them as sarcomas, sometimes as carcinomas.

These latter names probably contributed to the bad reputation of the lesions, and may be responsible for the prevailing opinion that they are particularly prone to undergo "sarcomatous and carcinomatous change."

Meticulous histologic examination led to many errors of deduction, such as Volkmann's opinion that the tumors were derived from endothelium, and to a peculiar descriptive nomenclature, that arrived at such excesses as "chondro-myxo-hemangio-endotheliosarcoma." In many cases, as in that just cited, the name committed the user to the endothelial theory of origin.

The numerous and confused tissue components had been noted by Johannes Müller, but never satisfactorily explained, except that Volkmann supposed them to be the result of the remarkable modifiability and metaplastic versatility of the endothelium. The presence of cartilage in the tumors had puzzled Virchow, who noted that, although it was frequent in the parotids and submaxillaries, it was unknown in the histologically similar pancreas. He also noticed that it was usually localized in the parotid tumors, but diffused through the submaxillary tumors. In the parotids he also found it upon rather than in the glands.

This led him to speculate as to whether it might not be formed by the capsule of the tumor, but he was unable to find a single case in which such origin could be demonstrated. He observed the association of mucoid tissue with the cartilage, and its occurrence independently of it, and mentions Robin's rare case, in which adipose tissue and cartilage occurred in the same tumor (*L'union med.*, 1857, **100**, 409). Combinations of cartilage, mucous and glandular tissue were also observed, but not explained.

To the adherents of the endothelial theory of origin, all of these structural peculiarities were simply evidences of the already mentioned metaplastic versatility of the parent tissue, and if the observer found anything manifestly inconsistent with that idea he had made a misobservation.

Thus, if, as not infrequently happened, he thought he saw an epithelial pearl, surrounded by a zone of prickle cells upon a basement transitional rete, he was mistaking modified endothelium for

epithelium, and compressed and hyaline degenerated endothelial cells for an epithelial pearl. Sometimes it seemed as though the adherents of the theory must regard the endothelium as exercising an uncanny ingenuity to deceive the observer.

As early as 1878 Marshall ("The Development of the Cranial Nerves of the Chick." (*Quart. Jour. of the Microscopical Society*), 1878, **18**, 10) noted that some of the epithelial cells of the neural crest in the head region, went into the formation of the mesenchyme. In 1882 Clementz (*Diss.*, Bonn, 1882) expressed the opinion that the cartilage in mixed tumors of the parotid might be formed from the epithelial cells, and he was echoed by Orth (*Lehrb. d. spez. Path.*, 1882, **1**, 629).

Little attention was, however, paid to the suggestion until it was revived by Ehrich (*Beitr. z. klin. Chir.*, 1906, **51**, 368), who expressed himself as convinced that the epithelial cells of the salivary gland tumors undergo a mucoid degeneration, and thus give rise to a substance whose subsequent condensation and further chemical transformation result in cartilage. He was quickly followed by Alezais and Bricker (*Compt. rend. Soc. de biol.*, 1908, **64**, 380), who recalled that as early as 1888 Carrier (*Compt. rend. Soc. de biol.*, June 30, 1889) had studied "ramifying cells" in the cartilages of cephalopods, and their relation to chondrotomes. They believed similar ramifying cells occur in the tumors of the parotid glands. Masson and Peyron as well as Paviot accepted this view of the origin of the cartilage, and the opinions of all these authors produced such an impression that Ewing accepted them, and on page 708 of the 1919 edition of his *Neoplastic Diseases* he wrote: "It is no longer necessary to seek to account for it otherwise than as a product of the epithelium;" Boyd in his *Surgical Pathology* (1925, p. 228) follows in line.

Forman and Warren, who also incline to this view sum up the matter thus: "From a study of seven specimens of the so-called mixed tumors of the salivary glands, it seems probable that there is in the head and branchial region of the human embryo, mesenchyme which has been derived from the ectoderm, and that inclusion or misplacement of this ectodermal mesenchyme gives rise to the so-called mixed tumors of the salivary glands." Such a view is repugnant to most histologists as contrary to the idea of blastodermic inviolability that underlies most of their work. But Nicholson points out the importance of abandoning this cherished theory in the hope of a better understanding of tumor origin.

In 1882 Cohnheim, in his *Vorlesungen ueber allgemeine Pathologie*, wrote: "The rudiments of the enchondromas of the parotid region consist of unappropriated particles derived from the cartilaginous parts of the branchial arches," and in the same year Volkmann produced evidence to show that the carcinomas of the neck arose

from epithelial vestiges. Little attention was paid to their work for twenty years.

A paper by Cuneo and Veau, read before the Congrès internationale de médicine in Paris, 1900, and later followed by Veau's thesis (1901) entitled, "Etude de l'epitheliome branchiale du cou: Branchiom malin de la region cervical" was the starting point of the revival of Cohnheim's theory. The latter contains an excellent review of the embryology of the neck, a personal study of 6 deep cervical tumors and a review of 42 cases collected from the literature, accompanied by excellent reasons for believing that the tumors arose through local defective development of the parts in which they occurred, as the result of "enclavement" or the isolation, sequestration and subsequent vegetation of some of the embryonal material.

They were supported by Deystieux, in 1903. Siegel also supported the theory, and divided the study of the tumors into: (I) A historic period, during which surgeons encountered the tumors but did not know how to account for them; (II) a scientific period, in which their explanation was complete.

Some relation between the mixed tumors of the salivary glands and the cervical tumors seems to have occurred to several earlier thinkers. In the discussion of a case of "parotid tumor of branchial origin," presented before the Montpellier Medical Society by Massabouau, Tedenet remarked that his pupil, Brintet, in his graduation thesis mentioned certain facts about the branchial origin of the tumors, antedating both Cuneo and Veau; both Vignaud and Moriquaud, as well as Morestin, refer to the thesis, "Tumeurs mixtes de la voile du palais," by Pitance (Paris, 1897), as committing him to their embryonal origin.

The structural resemblances between the mixed tumors of the salivary glands, the neck, the vault of the palate and the lips, the embryonal complexity of the regions in which they occur, their extreme rarity in the sublingual glands (Heineke found only 3 cases reported in the literature) and their complete absence from the pancreas, combine to impress one with the validity of the theory that is fully able to explain all of the puzzling histologic peculiarities of the mixed tumors without recourse to the imagination.

If the mixed tumors are "enclavomas" and most of them branchiomas, and originate in sequestrated and isolated embryonal material, the varying miscellany of tissues explains itself through the number and character of the originally sequestered materials. Antecedents of all of the different tissues found were present in the rudiment, or primordium, from which the tumor grew. No surprise at the presence of cartilage need be felt, for chondroplasts ready to produce it were contained in the rudiment. If no cartilage can be found it is because in that case no chondroplasts happened to be sequestered. The epithelium neither surprises one by

its presence or by its character. If it occurs as an imperfect gland-like structure, it probably means that some cells destined to form the salivary gland were included; if it is squamous, with or without pearly bodies, or with or without prickle cells, it probably means that ectoderm, destined to be part of the squamous epithelium of the mouth, or even of the external integument, was sequestered in the rudiment of tumor formation.

If some of the tissues composing the tumor are mature and normal, and other immature and embryonal in appearance, the difference may easily be accounted for. As accident determines that there shall be any sequestered embryonal substance, and if any, of what elements it shall consist, so mere accident may account for the fact that any or all of the sequestered elements survive and later vegetate. The sequestered embryonal material may be compared to plants in a badly arranged garden, some of which, growing rapidly and producing a dense foliage, suppress the more delicate and more slowly growing flowers. In these tumors the most numerous and most strongly vegetative elements may be supposed to mature most quickly and suppress the more delicate, which, in turn, may succeed in a later development, after death and degeneration may have overtaken their more vigorous antecedents. So the structure of the tumors may be conceived as varying from time to time, and thus may be explained some of the vagaries of growth.

It is from this point of view that the tumors are considered in this writing, and it must be kept in mind when, later, individual tumors are considered that behaved as mixed tumors but had the histology of sarcoma or of carcinoma, and when there are mentioned, as related to mixed tumors, certain carcinomas in which no indications of antecedent mixed tumors can be found.

Attention is called to the fact that an "enclavoma" is not necessarily a "branchioma." The latter is a special form of enclavoma deriving its embryonal material from the branchial arches. Some of the mixed tumors of the region under consideration may be branchiomas; others may not be.

It goes without saying that if adenomas and carcinomas of other organs can arise through transformation of the respective glands, and if sarcomas of other organs can arise through overgrowth of the connective tissues of those organs, there is no valid reason why adenomas, carcinomas and sarcomas of the salivary glands may not do the same. Not all of the tumors of these organs are mixed tumors; experience, however, seems to show that most of them are.

Chevassu (*Rev. d. chir.*, 1910, **41**, 145) takes pains to point out other possible sources of origin for the tumors, and mentions the following as worthy of consideration:

1. From the tissue of the gland itself.
2. From embryonal glandular rudiments by enclavemant.
3. From the branchial arches (Virchow thought the cartilage

might be derived from Meckel's cartilage; Hinsberg, from Reichert's cartilage).

4. From "embryoma juxta-salivaire," the theory of Forgue and Massabuau.

Weisshaupt, in 1912–1913, through studies of the embryology of the parotid gland, came to the conclusion that the *ramus mandibularis* may furnish the particular embryonal material from which tumors of the organ may grow, and Hans Moral, a year later, in an exhaustive study of the earliest developmental stages of the parotid and submaxillary glands, fully agreed with her, as he stated in a footnote appended to his paper.

But these glandular rudiments probably do no more than furnish the starting point of the adenomas and carcinomas or contribute the epithelial elements of the tumors. The mixed tumors are far too complicated to be so explained.

The mixed tumors, especially of the parotids, are so mixed, *i. e.*, so compounded of many different tissues, both embryonal and adult, both healthy and degenerated, in such varying proportions, that there can be no definite standard of histologic structure. This results in some uncertainty as exactly what tumors are or are not truly "mixed tumors."

Of the tissues found, the following may be mentioned:

A. Connective Tissues. 1. *Cartilage.* This may be hyaline, fibrous or yellow elastic in type. It may be embryonal or mature, inactive or growing, or it may be undergoing mucous degeneration. It is not always present, but when it is it may occur in any variety or combination of varieties, and forms so striking a feature that some have looked upon it as diagnostic in importance.

2. *Mucous Tissue.* This may be typical embryonal mucous tissue with the characteristic "spider-like reticulum," or a bastard tissue resulting from mucous metamorphosis of cartilage, fibroconnective tissue or epithelium. It may constitute the greater part of the tumor.

3. *Fibrillar Connective Tissue.* This is, of course, present in all of the tumors and varies greatly in quality It may be coarse and dense, blending with the perichondrium, or it may be fine and loose, forming a reticulum blending with the spider-like reticulum of the mucous tissue. In a few cases it constituted the greater part of the tumor which was described as a fibroma in consequence.

4. *Bone.* This is a rare component of the mixed tumors of the salivary glands. Tourneaux (*Bull. et mem. Soc. anat. de Par.*, 1913, **88**, 206) found bone in a mixed tumor twelve years old, the size of a fetal head. Gulicke (*Arch. f. klin. Chir.*, 1906, **81**, 275) found "osteoid" tissue in 2 tumors of the parotid. Schilling (*Beitr. z. path. Anat. u. z. allg. Path.*, 1921, **68**, 139) found bone in 1 tumor.

5. *Adipose Tissue.* This seems to have been observed only once, by Robin (*L'union med.*, 1857, **100**, 409).

6. *Muscle Tissue.* The only case in which this seems to have been observed is that reported as a "rhabdomyoma of the parotid," by Prudden (AM. J. MED. SCI., 1883, **111**, 409).

7. *Lymphoid Tissue.* This is not common, but may occur.

B. EPITHELIAL TISSUE. 1. *Glandular Epithelium.* Almost every mixed tumor of the region under consideration contains more or less of this important tissue. It is sometimes arranged so perfectly according to the pattern of the salivary gland as to cause the tumor to be described as an adenoma, but usually is atypical in detail, the gland-like units being large, unequal in size and not infrequently more or less filled with papillary excrescences. Such cases are more apt to be called cyst adenomas or cystic adenomas, or if one glandular space be very large it may be mistaken for a cyst. This probably explains why the removal of a cyst from the parotid may later be followed by recurrence in the form of a mixed tumor.

But usually there is little resemblance between the epithelial arrangements found in the tumors and in the glands. That is exactly what should be expected, the tumors being in but not of the glands.

The gland-like elements usually consist of comparatively few small rounded spaces lined with low columnar or cuboidal cells. They may be numerous or only occasional amid clusters of irregular cuboidal cells of peculiar appearance. When they are numerous they are responsible for the opinion that the tumors are adenocarcinomas, which is, of course, a mistake.

2. *Squamous Epithelium.* A great many, perhaps the majority, of mixed tumors contain considerable numbers of peculiar cells that are, perhaps, best called by the name first applied by Bosc and Jeanbrau, "indifferent cells." They are short spindles, and not in immediate contact, but arranged parallel with one another, to form sheets and strands that surround and penetrate into the lobules of the tumor tissue, so as to blend with its other cells, and lead to the impression that they are transitional and identical. These are the most subject to controversy of all the elements that enter into the composition of mixed tumors.

It was on account of their uncertain nature that they came to be looked upon as of endothelial derivation and the tumors called endotheliomas. But if they be studied carefully, in appropriate cases they may be found imperceptibly to become larger and more polyhedral, and more distinctly to become separated from one another by uniform intervals, across which delicate protoplasmic filaments pass from one to another, leading to typical spinous cells of epidermoid appearance. Occasional, or even many, epithelial pearls may terminate the series, and satisfy the observer that he is dealing with true squamous epithelium. The epithelial pearls may be so numerous as to mislead the observer into believing that, instead of a mixed tumor, he is dealing with a true squamous-cell carcinoma,

Hyaline metamorphosis, both of the connective tissues and of the epithelium is frequent in mixed tumors. If it forms cylinders in the centers of groups of epithelial cells the tumors are sometimes described as "cylindromas." By the term, however, different authors undoubtedly mean quite different things, so that it is not to be recommended for scientific employment.

It would be supererogatory to burden this paper with further histologic consideration of mixed tumors in general, or with histologic descriptions of the 90 cases studied in particular. Much of the literature of the subject is made up of such tedious details, difficult to read and leading nowhere, unless it be to what appear to be errors, such as Volkmann's, that the tumors are derived from the lymphatic endothelium, or Ehrich's, that the cartilage is derived from the transformed epithelium, or to what is still worse, that certain of the tumors are sarcomas, other carcinomas. They are neither; mixed tumors are mixed tumors, and should be called by no other name.

In passing, it may not be *mal apropos* to call attention to the tenacity with which some still cling to the idea that all malignant tumors must be either sarcomas or carcinomas, as though pathology had not clearly demonstrated the existence of other varieties of malignant tumors—malignant neuroma and glioma, for example.

Of the 90 cases forming the basis of this contribution, 67 were unquestionably mixed tumors and 12 probably mixed tumors. The remaining 11 may have arisen from similar primordia or rudiments, and so have been related to mixed tumors, but they were not such in the ordinary histopathologic meaning of the term, and are introduced for the purpose of contrasting the different clinical behavior of the different groups.

Of the 90 patients, 83 were white and 7 black. As most of the literature is European, scarcely any mention is made of the frequency of the tumors in different races. Balm (*Brit. Med. J.*, 1912, i, 1292) and Yen (*J. Am. Med. Assn.*, 1915, **64**, 1238) have reported cases in Chinese and Street (*Brit. Med. J.*, 1913, i, 1047) and Davidson (*India Med. Gaz.*, 1910, **44**, 292) reported cases in Hindus.

Of the cases of this series the sex incidence was: Mixed tumors: males, 34; females, 42. Carcinomas: males, 9; females, 5.

Of a total of 378 cases collected from all possible sources, there were 187 females and 177 males.

Of the present series, 28 tumors occurred on the right side and 38 on the left. From other sources it was possible to collect 114 as having occurred on the right side and 135 on the left. Heineke mentions 1 patient as having had a tumor on each side. There can, therefore, be no doubt but that the tumors are more frequent on the left than on the right side.

All of the tumors were sessile, but De Rouville and Martin (*Bull. et mém. soc d'anat. de Paris*, 1904, **79**, 659) and Jones (*Tr. Path. Soc. London*, 1871–1872, **23**, 263) have reported pendulous tumors.

Large tumors, whether parotid or submaxillary may be pedunculated.

Predisposition has been looked for without success. Mumps has been suspected as a cause, but not one of the 90 tumor patients even suggested it as a possible factor.

In Cases 3, 11 and 12 the patients noted the appearance of the tumors after attacks of sore throat. Cases 10 and 21 attributed their tumors to antecedent diseased teeth. Case 74 referred her tumor to a severe twist of the neck. Case 22 first observed the tumor after an attack of typhoid fever. Case 47 had been operated upon many years before for a cyst of the parotid gland, but in all probability the cyst was the primary occurrence of the tumor in a cystic state, as numerous parotid tumors follow cysts, and parotid tumors are frequently cystic. The cysts are, however, peculiar, and are not as frequently supposed, simple retention cysts. Lecene (*Rev. d. chir.*, 1908, **27**, 1) studied a number of them carefully, and found that they had nothing to do with the parotid, but were branchiomas. A cyst examined by Noral (*Bull. et mem. Soc. anat.*, 1905, **80**, 802) was filled with a yellowish-brown substance that resembled boiled rice.

Ordinary traumatism as a predisposing factor must be rare, and the only references to it in the literature seem to be the cases reported by Delbet and Herrenschmidt (*Bull. d. l,Assn. franç. p. l'étude du cancer*, 1910, **3**, 41), and by Moreau (*Bull. et mém. Soc. méd. d. hôp. de Paris*, 1917, 3, s, **61**, 783), though Kennon states that a number of the cases he collected gave a history of having been struck on the side of the face.

It is usual to express the ages at which mixed tumors make their first appearance by decades rather than by individual years, and the following tabulation shows the experiences of various authors in this particular, together with the 90 cases herein discussed, and cases collected from the literature:

TABLE I.—AGES AT WHICH MIXED TUMORS FIRST APPEARED.

Decades.	Wood.	Wilson and Willis.	Judd.	Present series.	Cases from literature.	Totals.
1 to 10	4	0	0	0	4	8
11 to 20	1	9	5	13	29	57
21 to 30	13	15	7	22	42	99
31 to 40	8	16	12	25	31	92
41 to 50	9	9	9	14	24	65
51 to 60	4	1	4	4	16	34
61 to 70	3	1	4	4	11	22
71 to 80	0	0	0	1	2	3
						380

The youngest patient in whom a tumor was discovered was less than one year of age; the oldest, seventy-eight years of age.

The ages at which the operations were performed is naturally greater, and the decade distribution of 193 collected cases is shown in the table on page 816.

TABLE II.—AGES AT WHICH OPERATIONS WERE PERFORMED.

1 to 10	0
11 to 20	14
21 to 30	26
31 to 40	34
41 to 50	39
51 to 60	42
61 to 70	26
71 to 80	11
81 to 90	1
Total	193

The youngest patient operated upon was ten years, the oldest eighty-one years of age.

Congenital tumors of the salivary glands occur, but they are all said either to be sarcomas or angiomas. It is not known that they are related to the mixed tumors. However, that phase of the subject was not examined.

For convenience of study the 90 tumors of the present series may be arranged as follows:

TABLE III.—CLASSIFICATION OF THE 90 TUMORS OF THIS SERIES.

I. Benign. Mixed Tumors:			
A. Clinically and microscopically valid (females, 23; males, 21)	44		
B. Clinically valid, but microscopically doubtful	10		
Ba. Histologically like sarcoma (females)	5		
Bb. Histologically like carcinoma (females, 2; males, 2)	4		
Bc. Histologically like adenoma (male)	1		
C. Clinically valid, but without microscopic confirmation (females, 1; males, 2)	3	76	
II. Recurrent. Mixed tumors:			
D. Clinically and microscopically valid (females, 11; males, 8)	19		90
III. Malignant tumors:			
E. Carcinomas, not appearing ever to have been mixed tumors (females, 5; males, 9)	14		

In Groups A, B, C, D and E of the tabulation interesting and important differences may be noted with respect to the average ages at which the tumors of the respective groups first made their appearance, and in their average duration. This is shown in years in Table IV:

TABLE IV.—AVERAGE AGES ARRANGED IN GROUPS.

	A.	Ba.	Bb.	C.	D.	E.
Average age of the patient when the tumor was first discovered	34.77	39.00	27.50	34.50	29.56	51.76
Average duration of the tumor at the time of operation	10.00	2.88	1.37	12.66	8.28	2.50

The average duration of all cases, except those of Class E, at the time of coming to operation was seven years.

The shortest duration of a mixed tumor before bringing the patient to operation was two months; 2 other cases were three and

six months respectively. It seems difficult to believe that these tumors could have existed so short a time, but such are the statements of the patients regarding them.

The longest duration before operation was thirty-two years, and 3 of the tumors are said to have existed for that time and 1 for twenty-five years.

Recurrences took place in 25 per cent of the mixed tumors studied, or in 19 in all.

In 3 of these cases data is lacking, so that they could not be classified in the following scheme:

I. Condition after One Operation.

Case.	Date of operation.	Condition.
46	1914	No recurrence for nine years and three months then a small tumor appeared. It was destroyed with radium, since when there has been no return
52	1915	No recurrence for seven years; now has a tumor three years and six months old
55	1921	Has a recurrence three and a half years old
59	1925	Has a recurrence three months old

II. Condition after Two Operations

62	?	
	1910	No recurrence in fifteen years; living and well
45	1895	
	1910	No recurrence in thirteen years, when he died of apoplexy
58	1910	
	1912	No recurrence in twelve years, when he died of cardiovascular disease
47	1894	
	1916	No recurrence in ten years; living and well except for facial palsy
63	1915	
	1917	No recurrence in nine years; living and well
56	1911	
	1923	No recurrence in two years; living and well
61	1915	
	1922	No recurrence in two years; living and well
54	1908	
	1912	No recurrence in one year, when he died from unknown cause
48	1913	
	1925	No recurrence in one year; living and well
57	1921	
	1924	No recurrence in one year; living and well
60	?	
	1924	Received one radium treatment; living and well

III. Condition after Three Operations.

Case.	Date of operation.	Condition.
49	1904	
	1911	
	1915	No recurrence in ten years; living and well
50	1861	
	1892	
	1911	The patient could not be further traced; she was eighty-six years of age in 1911
53	?*	
	1909	
	1912	This patient has disappeared; she was a Turk and may have returned to her native home

IV. Condition after Four Operations.

51	1910	
	1912	
	1918	
	1924	No recurrence in one year; living and reporting to the hospital for observation at intervals

In those cases in which it was possible to examine the microscopic slides of both the primary tumors and the recurrences, no differences of importance between the two could be found. The pathologist who examined the tissue of the second tumor removed from Case 49 reported "carcinoma," but his diagnosis was not confirmed, and that the case was not of that nature is shown by the fact that she is today living and well, ten years after her third operation.

The know periods of freedom from the tumor following operation are as follows:

TABLE V.—PERIOD OF FREEDOM FROM TUMOR FOLLOWING OPERATION.

Group A.

	Cases.		Cases
16 years	2	6 years	1
14 "	1	5 "	4
13 "	2	4 "	5
11 "	1	3 "	6
10 "	3	2 "	3
9 "	2	1 "	5
8 "	2	Less than 1 year	2
7 "	4		

Group Ba.

7 years	1 case, living and well
5 years	1 case, living and well
4 years	1 case, living and well
3 years	1 case, living, but has constant pain

* First operation performed in Europe.

GROUP Bb.

16 years	1 case, died of cirrhosis of the liver
15 years	1 case, living and well
9 years	1 case, died of pulmonary tuberculosis
1 year	1 case, living and well

GROUP C.

11 years	1 case, living and well
9 years	1 case, living and well
2 years	1 case, living and well

The operative removal of mixed tumors, especially when in or closely related to the parotid, may be very difficult on account of the intimate relation to the branches of the facial nerve, the large bloodvessels and Stenson's duct, all of which the surgeon naturally desires to conserve.

No doubt bits of the tumor are frequently unintentionally permitted to remain and form the starting point of the recurrences. Such remnants, freed from the isolating influence of the natural capsule, grow irregularly and sometimes invasively, so that deeper tissues are reached and second and third operations made more difficult. Cases become inoperable because of the unusual depth to which the released and distributed growth descends, and its intimate anatomical relation with structures that may not be disturbed. The tumor then dissects, compresses and obstructs with resulting necrosis, ulceration and hemorrhage, characterizing a peculiar local type of malignancy having nothing to do with the invasive and metastatic qualities of the sarcoma and carcinoma. Death usually results from tracheal or esophageal obstruction, though it is difficult to determine just how the patients die.

The more remote the tumor is from important structures, the more easy it is to remove, and the less prone to recur.

Fifty-seven of the tumors of the present series are described as benign, and when any are said to be nonrecurrent, no more is meant than that they have not yet recurred. As such tumors have been known to reappear after thirty-two years, there can be no certainty as to what may happen in the future of any case, and conclusions are fallacious.

The patients usually experienced few symptoms apart from the mechanical effects of the enlargement and the unsightliness the tumor produced. Eight patients, however, were annoyed by pain that was sometimes continuous and burning, sometimes shooting and distributed. Case 22 at one time lost vision in the eye of the affected side for a time.

In 14 of the 90 cases the tumors are said to have grown slowly and continuously, and the patients were influenced to undergo the operation because of embarrassment in moving the head or opening the mouth

But that which brought 16 of the patients to operation, and was most feared by the surgeon, was accelerated growth of the tumors. The testimony on this subject is peculiar. Thus, 1 patient asserted that the tumor had grown rapidly for six years before operation; 2, for three years; 2, for two years; 6, for one year; 1, for eight months; 1, for five months; 2, for three months; 1, for one month. No microscopic explanation for the accelerated growth could be found. The supposition and fear of the surgeons, that the rapid growth depended upon some inherent change—some malignant transformation—was not borne out by the microscopic studies of the tissues.

The oldest tumor in the present series was that of Case 52, and reached fifty years. Wood mentioned one that attained to an age of fifty-three years (his Case IV). Van Leewen (Virchow's *Arch. f. path. Anat.*, 1912, **207**, 330) observed one fifty-two years of age that had not changed during fifty years; Planteau (Thèse, Paris, 1876) described 1 that had existed for forty years. There seems to be no difference in histologic structure between very old tumors and others.

The largest tumors in the present series were those of Cases 36 and 38. The former grew to the size of a grape-fruit in seven years, the latter in eighteen years.

The largest tumor on record seems to be one in the parotid, reported by Conterill (*Scottish Med. and Surg. J.*, 1907, **20**, 526). It was more than twice the size of the patient's head, and is said to have weighed 26 pounds. It was not operated upon.

The largest tumor to be surgically removed from the parotid seems to be that reported by Street (*Brit. Med. Jour.*, 1913, i, 1047). It weighed 7 pounds and 3 ounces. It divides the honors, however, with W. W. Keen's case (*Trans. Coll. Phys. Philadelphia*, 1904, **26**, 83), whose tumor weighed 7 pounds, having grown rapidly after manipulation six years before.

The largest tumor to be removed from the submaxillary seems to have been that reported by Morestin (*Cong. franç. d. chir.*, 1905, p. 1140). It was as large as the patient's head, and weighed 6570 gm.

The sequelæ most to be feared after otherwise satisfactory operation for tumors of the parotid region are facial palsy and salivary fistula.

Interrogation upon these points was not contemplated in the follow-up correspondence, but 3 of the patients of this series complained of facial palsy following the operations, and 1 of a small fistula, in their letters.

F. C. Wood summarizes the results of his investigations in these words:

"Considering the mixed tumors of the face and neck as a group, we may say that an average of 25 per cent undergo changes which

express themselves in a clinically malignant course, while about 30 per cent recur after operative removal, though some of these recurrences may be stayed by a second and more complete removal. The records of my own series are somewhat different. Out of 37 cases in which notes of the patient's condition after operation have been recorded, 17, or 45 per cent have recurred locally. In 4 of these cases either internal metastases were soon apparent, or the local conditions were so serious that the patients either died from operative shock, as in 2 cases, or became inoperable from invasion of the bone and deep tissues of the neck. Of the remaining 13 cases, 1 is still alive after many operations, but will probably succomb to the growth, which is now beyond removal. In 12 cases, then, or nearly 33 per cent, there were local recurrences which were checked by operation, so that a second removal should always be attempted if the anatomic conditions permit of a complete removal of the growth."

In 1910 the pathologic staff of the St. Mary's Hospital, Mayo Clinic, engaged in an exhaustive study of mixed tumors, and Judd wrote as follows:

"We have operated upon 41 cases of true mixed tumors of the parotid. In 9 of these cases the endothelial element predominated (Volkmann's endothelial theory was popular when this was written); 5 were sarcomatous and 3 were mixed-cell tumors undergoing sarcomatous change. Ten of the patients came to us with recurrences or they had recurrences following our operations. Twenty-seven of the 41 patients have recently been heard from; 24 of them state that they are perfectly well and 3 of them say that they have a local recurrence; 2 of the 3 had preponderating sarcomatous elements at the time of operation; 1, a man, aged seventy years, had had a tumor for thirty years, with the history of rapid growth during the last three months. The patient died evidently of metastasis."

Wilson and Willis, studying the same series with later additions, wrote as follows (AM. J. MED. SCI., 1912, **143**, 656):

"Of 56 mixed tumors of the salivary glands that have been removed at St. Mary's Hospital, Mayo Clinic, from January 1, 1905, to April 10, 1911, 13 had been operated upon before they appeared at the Clinic. They, therefore, represented recurrences. Of 42 cases heard from since operation, 9 have had a recurrence of the disease; 5 of them were cases in which the neoplasm was of the loose markedly sarcomatous type, and 4, cases in which the original growth was of the hard fibrous type; 5 of these 9 cases have died; of the 5, 2 cases had tumors with a large epithelial element, and in 3 the largest element of the tumors was of sarcoma type.

"All of these cases have died away from the Clinic, and no opportunities have been afforded to make postmortem examinations.

"As has been pointed out by Judd, the recurrences are caused by

the difficulty of removing all portions of the tumor, yet preserving the fibers of the seventh nerve. When a tumor is already sarcomatous or carcinomatous at the time of operation the chances for recurrence are materially increased."

In 1921 Sistrunk again went over the cases from the Mayo Clinic that had then reached the number of 66, all of whom were traced (*Surg. Clin. North America*, October, 1921, 1515):

"Sixty-six consecutive patients were traced, upon whom primary operations had been performed from one to five years previously, and 37 patients on whom operation had been performed for recurring tumors. It was found that 93.4 per cent who had primary operations were alive, 18.3 per cent with recurrences and 6.6 per cent are dead; 89.2 per cent of the patients operated upon for recurring growths are alive, 37.8 per cent with recurrences and 10.8 per cent are dead. There were no deaths following operation in this series. The most serious complications following operation are partial or complete facial palsy and salivary fistulas. Sixteen of the 66 patients on whom primary operations were performed had temporary paralysis for from six weeks to one year; 1 patient had permanent partial paralysis and 1 permanent complete paralysis. Sixteen of the 37 patients operated upon for recurring growths had temporary paralysis, with a return of the function of the nerve after periods varying from six weeks to one year, while 29 of these patients had permanent complete paralysis and 5 permanent partial paralysis. One of the patients who had a primary operation developed a salivary fistula which has persisted for five years and nine months, and 1 patient operated upon for a recurring tumor developed a salivary fistula that has persisted for seven years. Tumors of the parotid gland were 11 or 12 times as frequent as those of the submaxillary gland."

The experiences of these investigators coincide with those of their predecessors, and vary but slightly with those resulting from the study of the present series. They, however, contained certain statements made with considerable assurance that seemed to need further elucidation and led to the questions that were the starting point of this research.

I. Does the Varying Histologic Structure of Mixed Tumors Regularly Enough Coincide with Their Subsequent Clinical Course to Permit a Reasonably Accurate Prognosis to be Made after a Microscopic Examination? Wood was able to divide his tumors into certain groups, and make deductions, as follows:

"1. Very fibrous tumors, with little cellular structure and with very little mucous degeneration and no cartilage.

"2. Very hard tumors, containing large masses of cartilage and but little connective tissue or cellular parenchyma.

"3. Soft, very cellular growths, with transparent trabeculæ of

mucous tissue surrounding areas which are opaque and yellow, which on microscopic examination will be found to be dense cellular areas, the color being occasionally, but not always, due to fatty degeneration or necrosis of the cells.

"The first and second forms are likely to be benign in their clinical course, while the third is likely to recur locally or to run an exceedingly malignant course."

It will at once be seen that this was a gross morbid, and not a histologic, grouping. In the present research it could not be adopted because the most desirable material was the oldest, and most of it consisted only of microscopic sections and case histories.

Kennon divided his cases into histological groups. The first he calls Adenomata, though stating that it corresponds to the mixed tumors. Of these he had 91 of which he traced the postoperative history of 32; the second were the carcinomata, of which he had 27 and traced 7; the third sarcomas, of which he had 6 and traced only 1. He therefore followed up a total of 40 cases as compared with the 90 cases in the present contribution.

As it is upon the microscopic appearance rather than any other factor that the surgeon and pathologist depend for prognosis, it was to that aspect of the subject that attention was directed. It was conceived that if every histologic component of every tumor was recorded, and its proportions to the totality of components estimated, the differences between the simple and recurrent tumors would appear.

But the general inequality and variability of the tumors resulted in complete inability to divide them into classes, or to show any essential differences between the recurrent and the nonrecurrent cases. There are, in reality, no differences of histologic structure between the recurrent and nonrecurrent tumors, because they are not different tumors, but tumors whose differing and peculiar environment alone determines that some may be easily and totally removed, while others are so situated that it is difficult or impossible to remove them completely.

From the study of this long series of cases, all of which have been so carefully followed, the conclusion is reached that *nothing of prognostic value results from the microscopic study of a mixed tumor*. This seems like a very strong statement, but it is believed that the reader will be convinced that it is warranted.

Reliance upon the microscope alone leads to such results as these:

CASE 6.—Miss S. H., white, at the age of eighteen years, discovered a tumor on the left side of the face in the parotid region. It grew slowly to the size of a walnut, when it was surgically removed, February 5, 1910, and called a "fibroid." Microscopic examination resulted in the diagnosis of "myxochondro-endothelioma of the neck." Later the hospital pathologist seems to have reviewed the section, as the diagnosis was changed to "adenocarcinoma of the parotid."

When the sections were studied as a part of this research, areas were found that bore a fair correspondence to what is called "cylindroma," but in others the resemblance to carcinoma was so striking that the tumor was classified as a carcinoma, pending the clinical follow up. The patient is now living and well, without recurrence, and having had no other operations, sixteen years after.

CASE 8.—Mrs. E. C., white, at the age of fifty years, noticed the appearance of a small tumor just below she left ear. It grew slowly, and in the course of six years attained the size of a walnut. It is said sometimes to have been larger, sometimes smaller. It was excised, October 14, 1914, and the pathologist to the hospital made a diagnosis of mixed tumor, which he subsequently corrected to "carcinoma."

Examination of six different parts of this tumor showed in all more or less distinct histologic appearances of carcinoma, though no conclusion was reached as to its variety. Malignant behavior was expected, but when the patient was heard from it was found that she had lived for five years without any return of the tumor, and had died of pulmonary tuberculosis.

CASE 13.—Miss M. J. G., white, at the age of forty-five years, observed a tumor in the left parotid region, which grew very slowly for fifteen years, then more rapidly for five years, and then very rapidly for two months, when it was excised, August 31, 1916. It proved to be both cystic and hemorrhagic. The hospital pathologist made a diagnosis of mixed tumor.

A total of twelve sections from four different parts of the tumor were examined, and revealed areas of such distinctly carcinomatous appearance that this tumor was at once placed in the carcinoma group. Nine years after the operation this patient is living and well, without recurrence, never having had other operations.

CASE 41.—J. S., a white man, aged sixty-three years, two years before operation, in February, 1920, found a tumor in the parotid region. Upon microscopic examination, it was diagnosed "endothelioma" by the hospital pathologist. Later studies of the sections showed the tissue to be partly composed of groups of distinctly carcinomatous cells in larger and smaller nests, surrounded by hyaline fibrillar tissue. It was looked upon as a highly malignant tumor, and placed in the carcinoma group, but at present, four years after operation, the patient is living and well, without recurrence, and having had no other operations.

Let it be noted in passing, that if these interesting cases had enjoyed the distinction of publication, of which many might have thought them worthy, they would now appear in the literature as carcinomas of the parotid. There is nothing so unfortunate to the study of tumors as the premature publication of cases.

But if histologic evidences are to be given any weight, they surely indicated that in these cases recurrence would occur, be followed by invasion of the lymphatics, and eventually kill the patient.

II. DO MIXED TUMORS FREQUENTLY BECOME SARCOMATOUS, AS THEY ARE COMMONLY SAID TO DO? Before proceeding with this problem, it may not be ill-advised to define sarcoma, so that the reader may know exactly what is meant by the term, which, with the amplification of knowledge is being more or less modified.

As it is herein used, sarcoma is a tumor composed essentially of cells of mesoblastic derivation and of rapid multiplication. It is fairly well circumscribed, but not necessarily encapsulated, and it tends to recur again and again, eventually distributing its cells to other parts, rarely through the lymphatics, but commonly through the venous system of bloodvessels which it invades.

Mixed tumors contain varying quantities of cellular tissues of different kinds. Among them are the "indifferent cells," which in their most primitive form appear very much like the short spindles of sarcoma, and when present in unusual numbers give the impression of sarcoma. Of course, the greater the number of cells, the greater the resemblance to sarcoma becomes. When the opinion that these cells were derived from the endothelium prevailed it was but a step to sarcoma; but with the discovery that these cells are in all probability embryonal epidermal and epithelial cells, their presence has no significance with regard to the sarcomatous nature of the tumor in which they occur.

The only test by which the correct conclusion can be reached is the discovery that the clinical behavior of the tumor appearing like sarcoma shall conform to the type.

Among the 90 tumors embraced in this research there were 7 that more or less distinctly conformed to the microscopic requirement of sarcoma. Three of them, from Cases 54, 55 and 71, because of their long standing and physical qualities, are included among the mixed tumors; 4, from Cases 67, 68, 69 and 70 are placed among the "doubtful tumors" of sarcomatous appearance. Their clinical course and the follow up are not without interest:

CASE 54.—Mrs. M. H., colored, at fifty-eight years of age, was operated upon for a parotid tumor of "many years'" duration. It recurred, and she underwent another operation in 1912. At that time the growth was the size of a hen's egg, nodular and very hard. It caused some pain.

The histology of this tumor was unlike any other. It consisted of a dense tissue not unlike yellow elastic cartilage, divided into ill-defined lobules, toward the periphery of which everything disappeared but the cells—closely approximated short spindles.

Unfortunately this patient only lived one year, but her husband asserts that "the tumor never bothered her any more, and she died of something else." Of course there was no autopsy.

CASE 55.—Mrs. M. Z., white, aged sixty-four years, for twenty years had a tumor on the right side of the face. About three years before operation it began to grow rapidly upward toward the ear and downward toward the neck, and at about the same time shooting pains became annoying. The tumor was excised in 1921, when it was the size of two fists. It was partly hard and partly soft, and not deeply attached, but was found to involve the parotid and to dip into the zygomatic fossa.

In 1925 she wrote: "I have another tumor in the place where the first one was removed. It started to grow about eighteen months after the operation for the removal of the first one, and I suffer more pain than ever. It has become quite large and looks red."

CASES STUDIED IN THE PREPARATION OF THIS PAPER.

A. Clinically and Microscopically Mixed Tumors—Not Recurrent.

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
1. H. S. 7855	M.	24	W.	8 years	R.	Walnut	2-19-13	Deaver	Lankenau	Living, well 7 years
2. Rev. W. E. R. 13455	M.	59	W.	8 years	R.	Egg	2-16-19	Deaver	Lankenau	Living, well 6 years
3. A. R. 15077	F.	33	B.	2 months	L.		12-28-20	Deaver	Lankenau	Died of pneumonia; no recurrence in 5 years
4. F. E. 11549	F.	22	W.	3 years	L.		2- 7-17	Deaver	Lankenau	Living, well 8 years
5. M. A. E. 7190	F.	62	W.	32 years	R.		4-18-12	Deaver	Lankenau	Living, well 13 years
6. S. H. 5264	F.	25	W.	7 years	L.		2- 5-10	Deaver	Lankenau	Living, well 15 years
7. E. N. 9613	F.	49	W.	10 years	R.	Walnut	2-20-15	Deaver	Lankenau	Living, well 10 years
8. E. C. 8621	F.	56	W.	6 years	L.	Walnut	10-15-14	Deaver	Lankenau	Died of pulmonary tuberculosis; no recurrence in 5 years
9. A. McC. 3388	F.	48	W.	20 years	L.	Apple	3- 9-11	Frazier	University	Living, well 14 years
10. W. J. B. 6542	M.	55	W.	7 years	R.	Egg	3- 8-16	Martin	University	Died in 3 months of arteriosclerosis
11. H. H. P. 7505	F.	52	W.	8 years	R.	Walnut	9-17-17	Carnett	University	Died of heart disease; no recurrence in 7 years
12. A. R. 4040	F.	32	B.	4 years	R.	Walnut	4-18-12	Deaver	University	Living, well 13 years
13. M. J. G. 6866	F.	65	W.	20 years	L.	Lemon	8-31-16	Martin	University	Living, well 9 years
14. J. Q. 7952 44608	F.	58	W.	25 years	L.	Goose-egg	8-19-18	Frazier	University	Living, well 7 years
15. M. W. 7999	F.	43	W.	3 years		Egg	9-23-18	Frazier	University	Died; no recurrence in 3 years
16. F. S. 4492	M.	22	W.	6 months	R.		3-27-24	Ivy	Polyclinic	Living, well August 1, 1926
17. A. G. 4861	M.	26	W.	8 years	L.		9-11-24	Skillern	Polyclinic	Living, well 2 years
18. E. S. S. P. 7928	M.	30	W.	3 months	L.	Plum	10- 3-21	Müller	Polyclinic	Living; no recurrence in 4 years
19. M. McI. 2081	F.	26	W.	3 years	R.		3-27-20	LaPlace	Polyclinic	Living, well 5 years
20. H. D. 3122	F.	44	W.	15 years	R.	Orange	3-26-22	Jopson	Polyclinic	Living; Roentgen-ray treatments; no recurrence in 4 years
21. L. B. S. P. 1321	F.	32	W.	?	R.		Oct. 1914	Martin	Medico-Chirurgical	Living, well 11 years

S. P. 1321

22. B. D. 2052	F.	39	W.	10 years	L.	Lemon	11-24-24	H. Deaver	Kensington	Living, well 1 year
23. E. D. L. 8848	F.	42	W.	16 years		Walnut	6-28-22	Gibbon	Pennsylvania	Living, well 3 years
24. J. D.; S. 7838	M.	42	W.	20 years	L.	Walnut	2- 2-21	Gibbon	Pennsylvania	Living and well 4 years
25. C. K. 8638	F.	30	B.	12 years			3- 7-22	Gibbon	Pennsylvania	Living and well, 3 years, 9 months
26. A. C.; A. 5046	M.	35	W.	4 years(?)	L.	Walnut	6-26-16	Neilson	Episcopal	Living, well 9 years
27. E. M.; A. 6715	F.	50	W.	8 years	L.	Walnut	10- 5-15	Ashhurst	Episcopal	Living, well 10 years
28. J. C.	M.	35	W.	16 months	R.	8 gm.	3-28-10	Wainwright	Moses Taylor	Living, well 16 years
29. W. T.	M.	31	W.	3 years	R.	Small	1-30-15	Wainwright	Moses Taylor	Living, well 10 years
30. W. B.	M.	49	W.	5 years	R.	Walnut	11- 5-24	Wainwright	Moses Taylor	Living, well 2 years
31. P. T.	M.	45?	W.	20 years(?)	L.	Lemon	2-19-21	Wainwright	Moses Taylor	Living, well 5 years
32. M. W.	F.	42	W.	7 years	R.	Egg	Nov. 1923	Carnett	Phoenixville	Living, well 3 years
33. L. D. 2183	M.	46	W.	10 years	L.	Grape	12- 1-21?		Philadelphia	Living, well 4 years
34. E. M. 2433	F.	65	W.	32 years	L.	Lemon	3-20-22		Philadelphia	Living, well 3 years
35. W. H. 5594	M.	33	W.	6 years	L.	Walnut	12-11-24	Carnett	Philadelphia	Living, well 2 years
36. W. G. 6432	M.	59	W.	7 years	L.	Grape-fruit	8-24-25		Philadelphia	Living, well 4 months
37. J. H. 2806 Aut. 7206	M.	77	W.	10 years	L.	Grape-fruit	No operation	Carnett	Philadelphia	Died without treatment
38. M. W.; I.1704 L. 12011	F.	54	W.	18 years	L.	Grape-fruit	8-22-19	DaCosta	Jefferson	Living, well 7 years
39. C. J.; G. 14329 L. 11143	F.	43	W.	7 years	L.	Plum	2- 5-18	Despard	Jefferson	Living, well 8 years
40. M. J. C.; K.253 L. 13461	M.	51	W.	1½ years	L.	Plum	6-17-21	DaCosta	Jefferson	Died immediately after operation
41. J. S. B.; K. 5843 L. 14045	M.	65	W.	2 years			Feb. 1922	Shallow	Jefferson	Living, well 4 years
42. M. H.; K. 5981 L. 14088	M.	62	W.	32 years	R.	Orange	3- 2-22	Loux	Jefferson	Died of diabetes, 1925; no recurrence
43. R. Y.; M. 3244 L. 13437	F.	54	W.	25 years	L.	Walnut	6- 8-21	Snyder	Jefferson	Living; no recurrence in 2 years
44. N. K.; L. 3719 L. 14736	M.	28	W.	11 months	R.	Plum	11-21-22	Hearn	Jefferson	Living, well, no return, 4 years

CASES STUDIED IN THE PREPARATION OF THIS PAPER.—(*Continued.*)

B. CLINICALLY AND MICROSCOPICALLY MIXED TUMORS—RECURRENT.

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
45. B. C. R. 5240	M.	37	W.	20 years	L.	Egg	1-29-10	Deaver	Lankenau	Tumor recurred in 5 years, second operation, no recurrence in 13 years
46. Mrs. A. M. 9302	F.	38	W.	2 years	L.	Hazel nut	9-30-14	Deaver	Lankenau	Recurred after 9 years and 3 months
47. J. M. 13167	M.	67	W.	More than 30 years	R.	Walnut	6-19-16	Deaver	Lankenau	Small cyst removed 30 years ago, new tumor began to grow at once
48. Mrs. B. D.	F.	39	W.	20 years	R.	Plum	1913 1925		Pennsylvania	Twelve years after first operation the tumor began to grow again
49. Mrs. G. H. W.	F.	28	W.	25 years	L.	Walnut	1904 1911 1915	W. J. Taylor	Pennsylvania	Living and well 10 years after the third operation; no recurrence
50. Miss C. B.	F.	86	W.	36 years	?	Nut Almond Orange	1861 1892 1911		Pennsylvania	Died shortly after last operation, but not of the tumor
51. Mrs. E. DaC.	F.	35	W.	15 years			1910 1912 1918 1924	 Frazier Frazier Müller	University	Living; no recurrence 2 years after last operation
52. Miss A. S.	F.	23	W.	4 years	R.	Almond	1-18-15	Frazier	University	Recurred after 7 years
53. Mrs. V. C.	F.	23	W.	6 years	L.	Egg	Unknown 2- 2-09 10-18-12	 Frazier	University	Grew continually after each operation
54. Mrs. M. H.	F.	62	B.	Recurrence was 4 years old	L.	Egg	1908 1912		University	No recurrence after second operation; died 1913, but not of the tumor
55. Mrs. M. Z.	F.	64	W.	20 years	R.	Two fists	6- 8-21	H. C. Deaver	Episcopal	Recurred after 18 months, now has another large tumor
56. T. G.	M.	34	W.	Recurrence was more than 12 years old	L.	Walnut	7-28-23	Wainwright	Moses Taylor	Living, well; no recurrence in 2 years

57. T. S. . . .	M.	28	W.	Recurrence was 6 months old	L.	Hazel nut	8-30-24	Wainwright		Living, well; no recurrence in 3 years
58. G. S. . . .	M.	39	W.	Primary 6 years; recurrence 2 years	L.	Walnut	4-25-12	Wainwright	Moses Taylor	Died in 1924, 12 years after operation; no recurrence
59. Mrs. M. R. .	F.	45	W.	5 years	L.		3-18-25	H. Deaver	Kensington	Recurred in 3 months
60. H. S.; N. 3720 . L. 16410	M.	30	W.	8 years			10-18-24	Shallow	Jefferson	Recurred 1 year after the first operation; Roentgen rays after the second; no recurrence, 2 years
61. A. C.; L. 2089 . L. 14570	M.	24	W.	10 years	R.		8-23-22	W. B. Davis	Jefferson	Living, well; no recurrence 3 years after second operation
62. A. C. C. 3252 .	F.	56	W.	15 years	L.	Hickory nut	2- 2-10	Frazier	University	Living, well 15 years
63. H. P. 7454 . .	M.	36	W.	2 years	L.	Marble	8- 7-17	Martin	University	Living, well 8 years

C. Clinically Mixed Tumors—Microscopy Not Verified.

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
64. L. C. 10974 .	M.	54	W.	24 years	L.	Plum	6-19-16	Deaver	Lankenau	Living, well 9 years after operation
65. G. S. . . .	M.	55	W.	16 years	L.	Plum	6-19-16	Wainwright	Moses Taylor	Living, well 16 years after operation; no recurrence
66. Mrs. A. G. . .	F.		W.	8 years		Plum	4-11-23	Gibbon	Pennsylvania	Living, well 3 years after operation

CASES STUDIED IN THE PREPARATION OF THIS PAPER.—(*Continued.*)

D. Tumors of Microscopically Peculiar Appearance and Uncertain Diagnosis, but Probably Mixed Tumors.

I. Not Recurrent.

1. Histological Appearance Suggesting Some Form of Sarcoma.

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
67. Miss L. F. 13289	F.	28	W.	6 months	L. neck	Lemon	1-18-19	Deaver	Lankenau	Living, well; no recurrence in 9 years
68. Mrs. P. W. 14864	F.	33	W.	3 years	R.	Walnut	9- 9-20	Deaver	Lankenau	Living, well 5 years after operation
69. Mrs. C. T.	F.	40	W.	6 years	L.	Oyster	10-11-22	Deaver	Lankenau	Living without recurrence, 4 years after operation
70. Mrs. I. B.	F.	65	W.	2 years	R. neck	Orange	1-19-21	Baum	Lankenau	Living, well 5½ years; no recurrence
71. Mrs. M. A. 7917	F.	70	W.	Many years	R.	Fist	7-19-18 8-11-18	A. C. Wood	University	Died 2 years after operation of myocarditis; no recurrence

2. Histological Appearance Suggesting Carcinoma.

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
72. W. H. H. S. P. 258	M.	45	B.	1 year			3-11-18	Rodman	Medico-Chirurgical	Died of cirrhosis of the liver 16 years after operation
73. J. McG. 10818	M.	21	W.	2 years	R. neck	Egg	4-19-16	Deaver	Lankenau	Died of pneumonia complicating pulmonary tuberculosis, 9 years after operation
74. Mrs. D. C. 5908	F.	30	W.	1 year	R.	Egg	11- 4-10	Deaver	Lankenau	Living, well 15 years after operation
75. Mrs. E. P.	F.	19	W.	18 months	L.	Bean	11-24-24	Wainwright	Moses Taylor	Living, well; no recurrence, July 21, 1926

CASES STUDIED IN THE PREPARATION OF THIS PAPER.—(*Continued.*)

II. RECURRENT.

THESE ALL SEEM TO HAVE BEEN CARCINOMATOUS TUMORS. MOST OF THEM WERE OF PAROTID DERIVATION. SOME WERE PERHAPS SUB-MAXILLARY, SOME MAY HAVE BEEN BRANCHIOGENIC, AND IN THE NECK. NEARLY ALL OF THE PATIENTS ARE DEAD, DYING OR LIVING WITH RECURRENCES OR METASTASES IN LYMPH NODES OR LUNGS OR BOTH. SOME WERE SQUAMOUS-CELL TUMORS, BUT MOST OF THEM WERE OF THE GLAND-CELL TYPES.

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
76. J. D. 14759	M.	50	W.	2 years	R.	Egg	7-10-20 May 1924	Deaver	Lankenau	Living, no recurrence in 2 years and 2 months (July 19, 1926)
77. J. D. 15191	M.	51	W.	4 months	R. neck	Egg	1-13-21	Deaver	Lankenau	Recurred four times in 6 months and finally killed
78. H. M. 11907	M.	62	W.	6 months	R. neck		6-21-16	Deaver	Lankenau	Died of the tumor in 1924
79. J. M. M. 6561	M.	62	W.	15 months	L.		7- 8-11	Deaver	Lankenau	Died of the tumor 1 year later
80. Mrs. M. W. 6914	F.	27	W.	1 year	R.	Lemon	10-10-16	Martin	University	Died November 1, 1917, of the tumor
81. E. C.	M.	75	W.	4 weeks (?)	R.	Walnut	7-20-22	Alexander	Episcopal	Died of the tumor, never having improved after the operation
82. W. W. VanD. A. 6288	M.	52	W.	1 year	R.		10-27-19	H. C. Deaver	Episcopal	Never improved after operation and died of the tumor
83. H. W.	M.		W.		R.	Walnut	1917 1919 1920 1923	Wainwright	Moses Taylor	Received Roentgen ray treatments; no recurrence when last heard from, July 21, 1926

CASES STUDIED IN THE PREPARATION OF THIS PAPER.—(*Continued.*)

II. RECURRENT.—(*Continued.*)

THESE ALL SEEM TO HAVE BEEN CARCINOMATOUS TUMORS. MOST OF THEM WERE OF PAROTID DERIVATION. SOME WERE PERHAPS SUBMAXILLARY, SOME MAY HAVE BEEN BRANCHIOGENIC, AND IN THE NECK. NEARLY ALL OF THE PATIENTS ARE DEAD, DYING OR LIVING WITH RECURRENCES OR METASTASES IN LYMPH NODES OR LUNGS OR BOTH. SOME WERE SQUAMOUS-CELL TUMORS, BUT MOST OF THEM WERE OF THE GLAND-CELL TYPES.—(*Continued.*)

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
84. Mrs. D. H.	F.	50	W.	2 years	L.		6-16-06	Wainwright	Moses Taylor	Died of the tumor a few months after operation
85. Miss M. S.	F.	40?	W.	28 years	R.		1905 1915 1925	Deaver	Lankenau	Now receives Roentgen ray treatment; no recurrence at present
86. Mrs. S. L. 10355	F.	68	W.	2 years			6-27-24 2-27-25	Gibbon	Pennsylvania	Now dying with metastasis to the lymph nodes of the neck
87. A. C. 2187	M.	60	W.	8 months		Lemon	8-26-08	Hutchinson	Pennsylvania	Died in another hospital, 1919, supposedly of the tumor
88. Mrs. M. H.	F.	40	W.	More than 15 years		Orange	1919 1924	Bradley	Philadelphia	Now has recurrence and metastasis to cervical nodes and lungs
89. W. K.; A. 13925 L.4311	M.	65	W.				1909	Nassau	Jefferson	Died of cancer in less than 2 yrs.

E. ADENOMAS AND CYSTIC ADENOMAS, WHOSE RELATION TO THE MIXED TUMORS MAY BE CLOSE BUT MUST AT PRESENT BE SEPARATELY CONSIDERED.

Identification.	Sex.	Age.	Color.	Duration.	Side.	Size.	Date of operation.	Surgeon.	Hospital.	Result.
90. I. B. 3294	M.	68	W.	7 years	R.	Egg	Nov. 1923	Carnett	Philadelphia	Living and well.

The histology of this tumor is interesting. It is made up of two types of tissue. One is coarse and not unlike fibrocartilage. Much of it is hyaline, with small spindle cells plentifully sprinkled between the curving hyaline bundles. Other parts are entirely composed of closely approximated small spindle cells, among which are plentiful small bloodvessels composed of endothelium only.

This case certainly suggests "sarcomatous change" in a mixed tumor, but it is entirely too early to say. Another operation and the tumor may never be heard from again.

CASE 71.—Mrs. M. A., white, aged seventy years, for "many years" had a tumor on the right side of the face, but during the year before the last operation, on August 11, 1918, it grew rapidly to the size of the first, and became inflamed, tender and painful.

Microscopically it appeared to be a simple, highly malignant small spindle-cell sarcoma.

Two years later, at the age of seventy-two years, the patient died of chronic myocarditis, there having been no return of the tumor.

It is unfortunate that Cases 56 and 65 died so soon after the removal of the tumors; one and two years, respectively, of post-operative life are too short to permit correct deductions regarding the true nature of the tumors to be made.

The next four tumors were extremely puzzling. They were all definitely sarcomas, histologically, and might have been reported as such, had they excited particular interest at the time of removal:

CASE 67.—Miss L. F., white, aged twenty-eight years, for six months knew of the existence of a tumor of the left side of the neck, and for one month was worried because of its rapid enlargement to the size of a lemon. It caused no pain, tenderness, dysphagia or cough. It was red, hard and freely movable.

It was surgically removed in 1919, and its physical qualities led both the surgeon and pathologist to regard it as a sarcoma. Upon microscopic examination, the latter called it "large round-cell sarcoma."

It was found to be almost exclusively composed of cells, large in size and polyhedral in shape, with large, but variable, vesicular nuclei. The cells were not such as to permit admission to the class of lymphosarcoma, and many would no doubt have been satisfied with the diagnosis of endothelioma. The numerous karyokinetic figures and signs of nuclear deformation led to the opinion that the tumor was highly malignant. It was, in fact, supposed that the patient had died of the tumor, but upon tracing her it was found that in 1925 she was alive and well and had never had any return of the tumor, though she had been operated upon for goiter that year.

CASE 68.—Mrs. P. W., white, was thirty-one years of age at the time that she first observed a tumor over the right parotid gland. It grew slowly and steadily until it attained the size of a walnut, though it remained freely movable.

It was excised in 1920, and microscopic examination of its tissue resulted in a diagnosis of endothelioma.

Later examination of the slides showed the tumor to be largely composed of small cells of spindle shape, arranged for the most part in parallel bundles and sheets, dense for the most part, but occasionally separating into a loose

reticulum. They may have been "indifferent cells," or fibroblasts, but the appearance was highly suggestive of sarcoma.

Five years after operation, in 1925, the patient wrote that she "had had no more trouble with her neck."

CASE 69.—Mrs. C. T., white, was forty-four years of age at the time that she first noticed the left side of her face becoming swollen, and began to experience a dull aching pain in the region of the ear. Both the enlargement and the pain increased, but it was not until six years later that a physical examination revealed the presence of a firm nodular tumor just in front of the left ear. It was not tender, but it was attached to the underlying structures, and not freely movable.

At the operation, performed in October, 1922, "a firm fleshy mass the size of an oyster was removed from the anterior lobe of the parotid gland."

Histologic examination of the excised tissue revealed what appeared to be a lymphosarcoma invading the gland and destroying its tissue by pressure and crowding.

It is difficult to think of this case as other than lymphosarcoma, and, indeed, it may turn out to be that, but in July, 1926, four years after the operation, the patient wrote saying: "So far as I can tell, there has been no return of the tumor, though I have constant aching where it was." Four years should be long enough for a lymphosarcoma to assert itself.

CASE 70.—Mrs. I. B., white, was sixty-three years of age at the time that she first observed a small nodule on the right side of the neck, midway between the mandible and the clavicle. It was not tender, but it grew slowly and steadily, extending upward, and causing some pain and dyspnea as it increased in size. In two years it attained the size of an orange. It was removed January 19th, 1921, and was found to be sharply circumscribed and apparently encapsulated, so that it was removed with ease. When examined with the microscope, it was found to be entirely composed of small spindle cells in a state of rapid multiplication, and quickly overtaken by mucoid metamorphosis. The diagnosis was "malignant myxosarcoma."

On July 15th, 1926, her physician wrote that the patient was living and well, and that the tumor had never returned. In five and a half years a malignant myxosarcoma should have returned.

So among these 90 tumors there were 7, 5 in the parotid and 2 in the neck, all of two or more years' duration, occurring at twenty-eight, thirty-four, forty, sixty-two, sixty-five and seventy years of age respectively, 4 of which were accompanied with more or less tenderness, 1 of which was not circumscribed and all of which appeared upon microscopic examination to be, or to be closely, related to sarcomas, of which only 1 returned, though 2 of the patients died before enough time had elapsed to make certain what might have been the outcome. The remaining patients are living and well, six, five and a half, five and three years respectively, after operation.

These tumors, therefore, did not manifest the usual behavior of sarcomas, and in all probability were neither sarcomas nor malignant tumors.

Equally important is the fact that in not one of these cases was there any microscopic evidence that the tumor had ever been a

mixed tumor in the ordinary sense and undergone "sarcomatous change," though the twenty years during which the growth had existed in Case 56, and the "many years" it had existed in Case 65, afford opportunity for speculation upon that subject.

But personal experiences and opinions must always be controlled by the experiences of others as portrayed in the literature.

The publications upon sarcomas of the salivary glands and neck leave much to be desired, and are in a somewhat confused state. Most of them are case reports, accompanied by microscopic descriptions always subject to the confusion resulting from differing interpretations of what is seen and preconvictions as to the supposed origin of the tumors.

They are, for the most part, entirely devoid of critical analysis, and scarcely ever is there any "follow up," by which to control the diagnosis. The microscopic appearance usually satisfies both surgeon and pathologist, and the case is hurried into print.

But if the uncertainty of the diagnosis increases in proportion as the tumor departs from the customary behavior of sarcoma, the reverse is also true, and cases that conform to the requirements must be regarded as valid.

If the tumor be congenital, if it makes its appearance in early childhood, if it attains to a large size in a few months, if it recurs again and again at short intervals, and if it ends by destroying the life of the patient through metastasis to the lungs, the microscopic diagnosis of sarcoma receives weighty support.

Cases of sarcoma of the salivary glands reported in the literature are not numerous. Those occurring in the parotids may be traced through references given by Brandes (*Frankf. Ztschr. f. Path.*, 1920–1921, **24**, 400) and by Degen (Dissertation, Freiburg, 1900); those in the submaxillaries, through those given in the paper by Chavassu (*Rev. d. chir.*, 1910, **41**, 1450), 45.

The number of cases is, however, small, and the number that remains after eliminations following critical analysis very small indeed.

Two kinds of sarcoma occurrence are described: (1) Those that occur chiefly in childhood and seem to begin as sarcomas; (2) those that begin as mixed tumors and eventuate in sarcomas.

Kauffmann (*Arch. f. klin. Chir.*, 1881, **36**, 672) reported a sarcoma that occurred in the left parotid of a boy, aged ten years. It recurred in several places and caused death in two years.

Schaffer (Dissertation, Erlangen, 1896) reports a tumor of five years' duration, occurring in a white woman, aged forty-three years, that was excised from behind and below the left ear, that recurred again and again at intervals of one or two years, necessitating four different operations, becoming inoperable, growing to an enormous size and finally causing death with metastases to the pleura and lungs. In his paper he refers to 10 other cases that he

collected, but though they may be valid clinically, they are less satisfactory pathologically.

Degen is said by Brandes to have seen a case of bilateral sarcoma of the parotids. Delaine (*Rif. med.*, 1910, **34**, 792) reported 2 melanotic sarcomas of the parotid; Haggard (*J. Tennessee Med. Soc.*, 1919–1920, **12**, 419), another; Schiller (Dissertation, Erlangen, 1906), another, and added 5 collected cases which he, however, suspected were really tumors of the skin, though his own, he believed, to have been of the parotid gland. There were no pigmented tumors among the 90 cases in the present series.

What conclusion can be drawn from these studies supplemented by the review of the literature, except that sarcomatous change in mixed tumors is rare? One fairly definite case, Case 55, out of the 75 supposedly mixed tumors of the present series, 1.33 per cent, and very few valid cases from the literature.

III. How Frequently do Mixed Tumors Undergo Carcinomatous Degeneration? Satisfactory analysis of the cases in which histologic carcinoma was found is extremely difficult, if not impossible, to make. Among the 90 cases now under consideration, those showing it may be arranged as follows:

A. *Benign Mixed Tumor* in parts of which the occurrence of histologic carcinoma led to the erroneous prognosis of malignancy. Here may be placed Cases 6, 8, 14 and 41, all of which have already been considered and described above.

B. *Doubtful Tumors.* 1. With histologic structure, suggesting carcinomatous change in an antecedent mixed tumor, but with clinical course opposed to it:

Case 72.—W. H. H., white, aged forty-six years, was operated upon, March 11, 1918, for a tumor of the side of the face, of one year's duration. No gross description of the tumor is available. The microscope shows a picture perfectly characteristic of carcinoma, but here and there interspersed with what seem to be vestiges of the structure of mixed tumor.

The case was regarded as one of carcinoma resulting from change in a mixed tumor, and as malignant, but the patient lived for sixteen years, and then died of cirrhosis of the liver.

Case 85.—Miss M. S., white, aged forty-three years, was operated upon for the removal of a tumor of unknown duration, from the parotid region of the right side of the face, just in front of the ear, in Europe, in 1905. It recurred, and in 1915 a second operation was performed in this country. A second recurrence necessitated a third operation in 1923. The last operation was followed by Roentgen ray treatment, but when she was last heard from, in 1925, "the growth showed signs of returning."

Unfortunately, the operations having all been performed in different hospitals, only the material from the last was available for study. The sections showed the greater part of the tumor composed of tissue indistinguishable from carcinoma. At an edge, however, where the tissue had been lacerated, there was an appearance of papillary processes, so that the pathologist had called it a "papillary carcinoma," a designation suggesting antecedent mixed tumor. The so-called papilla, however, may

have been nothing more than fibrovascular axes of the tumor surrounded by the tumor cells, part of the epithelium having been torn away during the mounting of the section.

Twenty years of recurrences and operations is not like carcinoma.

CASE 83.—H. W., a white man, was operated upon for the removal of a tumor of the right parotid in 1917, 1919, 1920 and 1923. After the last operation he was given Roentgen ray treatments (July, 1926). He is living and well, with no recurrence, three years after the last treatments.

The microscope showed a carcinoma with no indication of antecedent mixed tumor. Here, again, nine years of recurrences and operations is not like carcinoma.

CASE 88.—M. H., a white woman, aged forty years, was operated upon fifteen years ago for the removal of a "cheese tumor" of the parotid. In 1924 she appeared with another tumor in the same position. It was said to be of two years' duration, but had already attained to the size of an orange.

Microscopic study of this tumor made upon material obtained by biopsy revealed a small alveolar carcinoma solidum, parts of which suggested development from adjacent parotid tissue.

There was nowhere any resemblance to what is seen in mixed tumors, and it is unfortunate that nothing at all could be found out about the "cheese tumor."

No surgical treatment was undertaken, but the patient was carefully treated with radium, and the tumor made to disappear. When she was ready to leave the hospital a roentgenogram of the chest showed what were supposed to be metastases in the lung. Later, in 1925, two marble-sized swellings were found in the right submental region. But supposing herself on the way to recovery, and being able to work, the patient left the hospital. In July, 1926, she was still living, with a swelling at the original site of the tumor, and none in the neck. She would permit no examination of the lungs or further treatment, so the true nature of this tumor must be determined by its future behavior.

2. With clinical history, suggesting carcinoma, with no microscopic suggestion of mixed tumor, but with a benign course as in the latter:

(*a*) With a long enough period of postoperative exemption to be conclusive:

CASE 73.—J. McG., a white man, aged twenty-one years, for two years had a tumor in the right side of his neck. It was surgically removed in 1916, and the surgeon believed that he had excised a mass of tuberculous lymph nodes the size of a hen's egg.

The macroscopic appearance, indeed, justified the opinion for the removed tissue measured 7 by 4 by 3 cm., and was composed of amalgamated nodules of pinkish color, with more or less central necrosis.

The microscopic examination resulted in a surprise both to the surgeon and the pathologist, for the tissue proved to be typical carcinoma. Nearly all of the tissue was epithelial, and made up of large nests of large cuboidal cells, some of which were in mucoid degeneration. The final diagnosis was branchiogenic carcinoma.

The patient recovered from the operation and for two years worked as a teamster. In 1918 he entered the United States Army, became a member

of the American Expeditionary Force, and, returning from France at the close of the World War, led a dissipated life. In the army he had contracted pulmonary tuberculosis, having frequent hemorrhages and suffering from emaciation. After a drunken debauch he suddenly developed pneumonia, from which he died, October 8, 1925, nine years after the operation for the removal of the tumor.

His mother, carefully interrogated, asserted that there had never been any return of the tumor, and that at the time of his admission to the army the examining officers apparently did not discover the scar.

CASE 74.—Mrs. D. C., a white woman, was thirty years of age at the time of operation, November 4, 1910, for the removal of a tumor from the left side of the jaw. One year before she had suffered a severe "wrench" of the neck, and after twenty-four hours of discomfort discovered a tumor. It caused no pain, but grew steadily larger. At operation it was "shelled out" from beneath the "lower margin of the parotid." It was firm, encapsulated, and measured 5.5 by 3.5 by 3 cm. On section, parts of it exuded a milky juice, and were soft and friable.

The preserved microscopic slides leave much to be desired, but it is quite possible to determine that the chief component of the tissue was squamous epithelium, mostly of the basal cell type, with few prickle cells, no epithelial pearls and little keratin formation.

In 1925, fifteen years after the operation, the patient was living and well, never having had any recurrences.

(*b*) With too short a postoperative period to permit satisfactory conclusions regarding recurrence or malignancy:

CASE 75.—Mrs. E. P., a white woman, aged nineteen years, in November, 1924, was operated upon for the removal of a tumor that had been present in the left parotid region for eighteen months. It was a small movable growth about the size of a bean.

Microscopically it was an undoubted carcinoma, and resembled scirrhus of the breast more than anything else. It was thought to be malignant, and recurrence was expected, but up to July 21, 1926, there was no sign of recurrence.

CASE 76.—J. D., a white man, aged fifty years, was operated upon, July 10, 1920, for the removal of a tumor that had appeared as a small nodule just below the angle of the right jaw, and grown to the size of a hen's egg in the course of two years. It was accompanied by some pricking sensations, and interfered with moving the head. It was free and encapsulated, though attached to the surrounding tissues here and there. On section, the naked eye gave the impression that it was cellular in structure and necrotic in parts.

Microscopic examination revealed a structure that was at first called endothelioma, but which was later regarded as carcinoma because many of the cells were found closely to resemble squamous epithelium, though no prickle cells could be discovered.

The tumor recurred, and a second operation was performed in 1924. up to July, 1926, there has been no return of the disease.

C. *Malignant and Fatal Tumor: Carcinoma.* The 10 cases in this group of carcinomas suffered from tumors that were certainly malignant, as with the exception of Case 86, who is suffering from metastasis and will die, all are already dead. These cases, therefore,

may serve as a basis of comparison, and a means of discovering such differences as may obtain between the way in which the truly malignant tumors originate and eventuate.

No cause is assigned for the appearance of any tumor except that of Case 82, who thought that it followed the extraction of the teeth.

Two of the patients complained of pain: Case 79, who suffered from facial palsy, referred it to the temple of the affected side; Case 81, to the neck and shoulder. In 2 cases it is expressly stated that there was no pain. As nothing is said about the symptom in the other cases, it may be supposed that it was either absent or unimportant. This is interesting as Kennon's cases all suffered from pain.

In 4 cases the growth of the tumors is said to have been gradual; in 2, rapid, in Case 89 it is said to have been slow at first, then more rapid.

Thus far the conditions are fairly parallel with mixed tumors, but a striking difference is noted when the duration of the tumors is considered.

If the tabulation covering the preoperative duration of the 90 tumors of the present series be referred to, it will be found that the average preoperative duration of the nonrecurrent tumors (Group A) is ten *years;* that of the recurrent mixed tumors (Group D), 8.28 *years;* and of the malignant carcinomatous tumors (Group E), eighteen *months.* The contrast between ten years and eighteen months is certainly very marked, and ought to furnish valuable prognostic data.

The same short period of preoperative duration is noted with regard to the carcinomas of the submaxillary glands by Delannoy and by Agrifoglio. The latter, indeed, makes the criteria for the differential diagnosis between mixed tumors and carcinomas, that the latter shall be of short duration, early recurrence and be followed by lymph-node metastasis.

In order that a mixed tumor undergo "carcinomatous degeneration," it is necessary that there first be a mixed tumor, and then that it "degenerate."

There are two means of recognizing a mixed tumor:

1. By its histology. This is the test usually applied, but as has already been pointed out, it is of questionable validity because of the confused and irregular structure of these tumors, on account of which false conclusions are frequently drawn. By itself it is inconclusive.

2. By its duration. Considered from the standpoint of averages, it would seem as though this should be a most valuable guide, but it proves upon investigation to be full of fallacies.

Instead, therefore, of depending upon a single factor, *structure and duration have to be considered together both in making the diagnosis and in deducing a prognosis.*

Three undoubted benign mixed tumors, if the testimony of the patients can be relied upon, were characterized by remarkably short preoperation durations (Cases 3, 16 and 18). Each had a histologic structure that anyone would accept as mixed tumor; each was composed of lobules of semicartilaginous jelly, between which were sheets and strands of indifferent cells. In none was there any suspicion of carcinoma from the histologic point of view, but the preoperative duration fell within the limits of carcinoma.

In 1, Case 16, the operation was performed so recently (two and a half years) that the outcome cannot be said to be certain; the tumor may return, and it is even possible that the tumor may turn out to be malignant, though such an event is not expected. In the other 2 the postoperative behavior (Case 3, five years and Case 18, four years of freedom from recurrence) clearly shows the tumors to be benign.

Four nonrecurrent mixed tumors have already been mentioned in which epithelial irregularities were found that led to the supposition that they were undergoing "carcinomatous change," and probably would turn out to be malignant. But their benign behavior, shown by their long postoperative duration has served to correct the deceptive microscopic appearances:

Case 6: Preoperative duration, seven years; postoperative exemption, sixteen years.

Case 8: Preoperative duration, six years; postoperative exemption, five years.

Case 14: Preoperative duration, twenty-five years; postoperative exemption, seven years.

Case 41: Preoperative duration, two years; postoperative exemption, two years.

In the following 2 cases the histologic picture of carcinoma was convincing, but the duration shows the diagnosis to be erroneous:

Case 72: Preoperative duration, one year; postoperative exemption, sixteen years. The former might easily indicate malignant tumor, but the latter totally disproves it, unless it be a case of carcinoma cured by operation.

Case 85: Preoperative duration, unknown, but the total duration, twenty years. There have been three operations and four occurrences of the tumor at intervals of ten years each, and she is now living with a recurrent tumor, not clinically carcinoma.

In the following 2 cases, the microscope shows no vestige of mixed-tumor structure, but their durations seem to indicate its antecedence.

Case 83: Total duration of the tumor, nine years, during which there have been four operations, and subsequent Roentgen ray treatments. The last operation was in 1923, and there has been no recurrence since. In spite of its distinctly carcinomatous appearance, this may be only a mixed tumor and remain benign.

Case 88: Fifteen years before coming for the last operation this patient had a "cheese tumor" removed from the side of the face. Upon admission she had a large tumor, the size of an orange. It was made to disappear under careful treatment in the radiologic clinic. Later she was thought to have metastases in the cervical lymph nodes and lungs.

This is an undoubted malignant tumor, but whether primarily, or as the result of "carcinomatous degeneration" of some vestige of the antecedent "cheese tumor," cannot be determined, as nothing can be found out about the latter.

In the following cases both the microscopic examination and the preoperative duration indicated carcinoma, but the course of events was a surprise:

Case 73: Preoperative duration, two years; postoperative duration nine years. Died of pulmonary tuberculosis complicated by pneumonia, without recurrence of the tumor.

Case 74: Preoperative duration, one year; postoperative duration, fifteen years. Living and well.

Case 76: Preoperative duration, two years; postoperative duration, two years. Living, no recurrence.

Of these, Cases 73 and 74 may possibly be cases of carcinoma cured by operation; Case 76 was too recently operated upon to be of value.

Among the malignant and fatal tumors 2 stand out because of the length of the total duration of the disease:

Case 78: Had a branchiogenic carcinoma of the neck of six months' preoperative duration. He died of the tumor nine years later, the intervening history not having been determined.

Case 87: This was an Italian with a tumor of the parotid, sections of which show close resemblance to squamous-cell carcinoma. One of his friends asserts that he died in some Philadelphia hospital, and of the tumor, but exactly when is not known. It was thought to have been about eight years after the first operation.

In the remaining cases (Cases 77, 79, 80, 81, 82, 84, 86, 89) no suspicion of mixed tumor antecedent to the carcinoma was aroused. All of these tumors developed within two years, and nearly all of them within one year. No suggestion of mixed tumor was found in the histology, and all of the patients were dead within two years after the first operation.

Accepting these tests of time, structure and behavior as indicating how many and which of the tumors under consideration may have begun as mixed tumors and undergone "carcinomatous degeneration," their number is found to be very small indeed, and finally boils down to 3 possible cases (Cases 83, 85 and 88):

Case 83: After four operations, extending over a period of six years, has enjoyed a postoperative exemption from tumor for two years, which is too short a time to permit final conclusions.

Case 85: Is still under treatment and observation after twenty years of suffering from the tumor, with no metastasis to prove it to be carcinoma.

Case 88: Is living with metastases to the cervical glands and lungs, but whose tumor may be a primary carcinoma, and in no manner related to the antecedent "cheese tumor," that may not have been a mixed tumor at all, but some more simple thing, as, for example, a sebaceous cyst.

From this lengthy analysis, therefore, it would seem as though these 90 cases furnish very little evidence in support of the statement that mixed tumors undergo "carcinomatous degeneration."

It would be very interesting to compare these case analyses with those of Kennon but it is difficult to do because of the brevity and inadequacy of his protocols. He thought that 35 per cent of his carcinoma cases developed from antecedent "adenomas"—*i. e.*, mixed tumors. But he depended upon the microscopic examination to reveal the carcinomatous nature of the process, and was contented with the subsequent inoperability or fatality of the tumor for confirmation of the diagnosis. In only one of the protocols (Case I) does he speak of metastasis to lymph nodes, which makes certain that it was carcinoma, and as that case had a preoperative duration of five years, it is possible that it originated in a mixed tumor. The protocols of the other 6 cases either suggest that the patients died from recurrence and inoperability of the mixed tumors themselves, or they throw no light on the subject. There seems to be no justification for his 35 per cent of malignant transformations.

Landsteiner (*Ztschr. f. Heilkunde. Abt. f. Path. Anat.* 1901, **22**, 1) says of mixed tumors: "They as easily undergo carcinomatous as sarcomatous change." The statement is probably true, though not in the sense in which he meant it, for he was supporting the ready transformations upon the basis of what he had found histologically.

The evidence rather points in the direction indicated by Löwenstein (*Frank. Ztschr. f. Path.*, 1910, **4**, 187). He believed that to pass from atypical epithelial proliferation to true, and especially malignant tumors, some special step is required.

But again individual experience must be supplemented by that of others, and since the literature contains so many intimations that mixed tumors may become carcinomas, it becomes important to find out what proofs of it may be forthcoming.

The literature of carcinoma of the salivary glands is in the same state of confusion that was found to diminish the value of the writings upon sarcoma. It is not possible to recognize the tumors under consideration by the names applied to them. What does a writer mean when, for example, he asserts that most of the mixed tumors turn out to be "adenocarcinomas?"

What does "carcinoma" mean when applied to a parotid tumor? A histologic structure or a clinical behavior, or both? What is an

"epithelioma" of the parotid? Just as the endothelioma theory of origin led to many of the mixed tumors being classified as sarcomas, so the return to older theories led many of them to be called epitheliomas.

But difficulties of nomenclature are not all that disturb the collector of facts. A large part of the literature consists of brief case reports hurried into print with details of the operation, an account of the microscopic examination of the material removed and with some seemingly appropriate name applied to it without the least suspicion that the lapse of time might prove the diagnosis to be doubtful.

Here is a good example of what is meant: "Probable Epitheliomatous Degeneration of a Mixed Tumor of the Parotid." The title was promising and the paper was found and read. It proved to be about a tumor of two years' duration that occurred in the right parotid of a woman, aged fifty years. It had recently grown rather rapidly from the size of an egg to that of an orange. It was removed, and shortly recurred. Another operation was performed. Upon microscopic examination, the tumor was found to be composed of mucoid, cartilaginous, adenocarcinomatous and sarcomatous tissues, with occasional epithelial pearls. Such structure is common in mixed tumors; mixed tumors recur in from 25 to 30 per cent of the cases. The history of the patient ends with the second operation. Where is the evidence of the "probable epitheliomatous degeneration?"

If mixed tumors did undergo changes by which they were transformed into carcinomas, one would expect them to evince the same manifestations of their new nature as are found among other carcinomas, *i. e.*, recur locally, but quickly give metastasis to the lymph nodes, and later to the lungs. The occurrence of metastasis may, therefore, be made the test of the true carcinomatous nature of any suspected tumor. What does the literature have to say upon this subject?

Tomassi (Virchow's *Arch. f. path. Anat.*, 1864, **31**, 111) observed a submaxillary carcinoma that had existed for eight years, and finally gave metastasis to the lymph nodes of the neck and to the lungs, pleura, liver and peritoneum; the liver weighed 12 pounds.

Chiari (*Anz. d. k. k. Gesellsch. d. Aertze in Wein*, 1879–80, **21**, 741) reported a "cystosarcoma phyllodes" (Joh. Müller) of the parotid with metastasis to the lungs (*Med. Jahrb. Wien.*, 1881, p. 1). Later (*Wien. Klin. Wchnschr.*, 1912, **25**, 1562) he mentioned a small submaxillary mixed tumor of thirty-five years' duration that became malignant and invaded the regionalcervical lymph nodes.

Senn (*Internat. Clin.*, 1902, **4**, 183) has reported a case of "malignant disease of the parotid and regional lymphatic glands," presumably carcinoma with metastasis, and as no history of the case is given, it may have arisen in an antecedent mixed tumor.

Wood's Case IV, which resembled a squamous-cell carcinoma,

gave metastasis to the cervical lymph nodes. His Case XLI, which was regarded as a sarcoma, gave metastasis to the lungs and skin. He had no other metastatic tumors.

Nasse (*Arch. f. klin. Chir.*, 1892, **44**, 233) observed 2 cases, 1 of which had a metastatic tumor in one cervical lymph node, the other "enlarged lymph nodes all down the side of the neck."

Brandes (*Frank. Zeitschr. f. Path.*, 1920, **24**, 400) observed a single case with metastasis to a cervical lymph node.

Pfender (*Med. and Surg.*, St. Louis, 1917, **1**, 366) reports a case treated by roentgenotherapy that died of metastasis. The tumor was of only eighteen months' duration, and there is no reason to suppose that it had been a mixed tumor.

Jouliard, among his 14 tumors of the submaxillary glands mentions an "encephaloid" that gave metastasis to the cervical nodes and left lung. As it was of sixteen years' duration, it may have begun as a mixed tumor, though it ended as a carcinoma.

Partsch (*Deutsch. Ztschr. f. Chir.*, 1923, **153**, 269) reported a "cylindroma" of the parotid, with metastases to the pleura. The secondaries occurred in the form of about a dozen flat and pedunculated cauliflower-like disks, varying in diameter from a dime to a quarter-dollar, and about 3 mm. thick, that were scattered over the surface of the otherwise unchanged pleura.

Porter and Churchill (*Surg., Gynec. and Obstet.*, Chicago, 1924, **38**, 336) reported a case of "malignant tumor of the parotid," which having been operated upon for recurrences some eight times, and suffered from two attacks of pneumonia, was found to have metastatic tumors in the thoracic cavity. As the primary tumor developed in one year, it probably was not a mixed tumor as here understood.

Berard-Moutet (*Lyon chir.*, 1914, **11**, 651) reported a case of parotid tumor with metastases to the temporal region and abdominal wall.

Rispal and Samiac (*Toulouse med.*, 1906, **8**, 121) have reported a parotid "cylindroma" with cranial metastasis, and Budde (*Centralbl. f. Chir.*, 1922, **69**, 1888), one of carcinoma cylindromatosus with metastasis to the femur, attended by pathologic fracture.

Griffini and Trombetta (*Atti. d. r. Accad. d. Torino*, 1883, vol. **18**) have also reported a case with metastasis to the bones.

Von Ewetzky (*Virchow's Arch. f. path. Anat.*, 1877, **69**, 36) observed a "cylindroma" with two recurrences, metastasis and death. It was, however, regarded as a plexiform sarcoma, and arose in the orbit and not in a salivary gland.

Gueit and Puech (*Bull. d. soc. d. sc. med. et biol. de Montpellier*, 1922–23, **4**, 52) report a case of metastasis from an "epithéliome" of the parotid to the spinal cord, but as the publication could not be obtained, it is not known what relation the tumor may have had to mixed tumor.

Forgue, Morgue-Molines and Villa (*Ibid*, 1924–25, **6**, 42) also

reported a mixed tumor of the parotid with multiple metastases to the skin after four years, but again it was impossible to consult the publication.

Does not the survey of the literature lead to the same conclusion as the case analyses, that carcinomatous degeneration of mixed tumors must be rare?

Conclusions. 1. The theory of "enclavement" or accidental sequestration of embryonal cells during the early and complicated development of the face and neck affords the most satisfactory explanation of the origin of their mixed tumors.

2. By that theory it is easy to account for the number and variety of tissues found in the tumors, and for their varying proportions and conditions.

3. Mixed tumors are individual entities, having no relation to the normal structures in which they occur, but from which they do not arise.

4. They have nothing to do with other kinds of tumors, and should be called "mixed tumors" and nothing else, regardless of their histology.

5. They are inherently benign, but commonly recur after excision, and if frequently disturbed become locally destructive and invasive, without giving metastasis.

6. The histology of mixed tumors is extremely complex, but on that account their microscopic diagnosis is usually very easy.

7. The immaturity, atypical arrangement and confused intermingling of the various tissue components easily lead to misinterpretations as to their nature and mistakes as to their dispositions.

8. Histologic variations among mixed tumors have no bearing upon prognosis. The microscope, beyond showing that the lesion is a mixed tumor, is misleading rather than enlightening.

9. The rapid enlargement of a mixed tumor of long duration and slow growth is not the result of malignant change.

10. Malignant change, whether "sarcomatous" or "carcinomatous," in mixed tumors must be rare, and its occurrence is difficult to prove.

11. As intervals of ten, twenty and even thirty years may elapse between the operative removal of a mixed tumor and its recurrence; caution should be exercised in declaring any case to be cured.

LITERATURE.

For the literature prior to 1904 the paper by Francis Carter Wood, "The Mixed Tumors of the Salivary Glands," Ann. Surg., 1904, **29**, 57, 207, with its 135 references leaves little to be desired.

The contribution of L. B. Wilson, and B. C. Willis, "The So-called Mixed Tumors of the Salivary Glands," Am. J. Med. Sci., 1912, **143**, 656, has appended 49 references to the literature between 1904 and 1912.

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THE DETERMINATION OF THE ICTERUS INDEX WITH CAPILLARY BLOOD.

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The yellow color of blood serum is largely due to its bilirubin content. The normal level of this pigment in the blood stream is chiefly determined by the natural destruction of red blood cells, the resulting liberation of hemoglobin, and the conversion of this hemoglobin into bilirubin. Factors which increase the destruction of red blood cells, or which interfere with the normal elimination of bilirubin from the blood will tend to increase the bilirubin content. On the other hand, in the secondary anemia following hemorrhage, with its diminution in the available hemoglobin, the bilirubin content of the blood will tend to be lowered. With this variation in the bilirubin content, there is a corresponding variation in the depth of color of the blood serum.

The value of using this intensity of color of the blood serum as an index of the bilirubin content of the blood, was appreciated by Blankenhorn.[1] He arrives at the bilirubin content by estimating the degree of dilution of the plasma which would still show pigment just perceptible in a column of 1 cm. depth. Meulengracht,[2] using the same principle, chose as his end point of dilution a definite color intensity of a known standard with which the diluted plasma was matched. For this purpose he used a 1 to 10,000 solution of potassium bichromate, and diluted the blood plasma with physiologic salt solution until it matched the standard. This dilution was represented by a number, which has come to be known as the icterus index. Meulengracht later devised an apparatus similar to the Sahli hemoglobinometer, for carrying out his test.

Both Blankenhorn and Meulengracht used blood plasma. Because of the slight opalescence observed in plasma (probably due to blood

platelets), and the time required for the blood corpuscles to settle out, Gram[3] suggested the use of serum (blood allowed to clot and then centrifuged) in its place. Bernhard[4] and Maue[5] further modified the test by making the determination with a colorimeter, using potassium bichromate 1 to 10,000 as a standard. Serum too intense to be compared with this standard is first diluted with physiologic salt solution. To simplify the test, Murphy[6] suggested the direct comparison of the serum with dilutions of potassium bichromate, corresponding to a scale of useful index values.

With these methods, studies have been made on the variations of the icterus index in health and disease. Using the technique of Bernhard and Maue, Bernheim[7] determined the icterus indices of a large number of cases. According to her studies, the normal index lies between 4 and 6, and remains remarkably constant for a given individual. About 15, clinical jaundice is manifest; below 15 invariably absent. The range between 6 and 15 represents jaundice not visible clinically. A knowledge of this socalled latent jaundice is an important aid in diagnosis. With the appearance of clinical jaundice the index rises, and in cases of intense jaundice may mount above 100.

The increasing appreciation of the value of the icterus index in diagnosis and prognosis and as a simple test for liver function raised the problem of an easier method for its determination. In order to carry out the test according to the procedures described above, it is necessary to remove from 3 to 5 cc. of blood from a vein, and if serum is to be used, the needle, syringe and tubes must be perfectly dry to prevent hemolysis. It appeared that a test which necessitated venipuncture would not come into general use as an everyday procedure. Dr. Ralph C. Larrabee, appreciating this disadvantage, suggested that a simpler test be worked out using blood taken by skin puncture. Of a number of methods studied, the following was found to be simple and reliable: a few drops of blood are taken up into a 2-mm. capillary tube, centrifuged, and the serum compared with standards contained in tubes of the same bore.

A number of determinations carried on by the capillary method checked very closely with determinations made simultaneously according to Murphy's method of direct matching of serum from vein with standards.[6] In the following cases the test compared favorably with the colorimeter method of Bernhard and Maue. Blood was taken from vein and skin at the same time.

Capillary (3-mm. tube).	Colorimeter.	Capillary (3-mm. tube).	Colorimeter.
3	2.6	10	11
3	3.4	10	12
4	3.8	22	25
5	4.5	25	23
6	5.4	30	32

For general use the 2-mm. tube is preferable to the 3-mm. tube. Less blood is required, and the determinations are sufficiently accurate for special studies as well as for clinical purposes.

Technique. Glass tubing of 2-mm. uniform bore is cut into convenient lengths and cleaned by immersing in 5 per cent nitric acid for twelve to twenty-four hours. The acid is thoroughly washed off in running water, and the tubing finally dried with alcohol and ether. This careful cleansing and drying of the tubes is necessary to avoid hemolysis. A supply of tubes of about 10 cm. in length with both ends drawn out to capillary size are then prepared with a Bunsen flame. Straight ends are preferable to those drawn out in S-shape fashion, as the clot may be caught in a curved end and there may be difficulty in throwing it down.

The tip of the patient's finger is wiped dry and an adequate puncture made to insure a few good sized drops. The first drop is wiped off with dry gauze and with gentle squeezing the blood is taken up into one end of a capillary tube held horizontally. Excessive squeezing must be avoided for it tends to produce hemolysis. If the first puncture does not provide sufficient blood, a second puncture should be made. A column of blood 2 cm. long is sufficient for an accurate determination. The blood is allowed to clot, and the opposite clear end of the tube sealed in the edge of a flame. With a tube 10 cm. in length there is no danger of heating the blood at the opposite end, which would cause hemolysis. The tube is placed sealed end down in a padded centrifuge tube, and the clot thrown down at slow centrifuge speeds (200 to 400 r.p.m.) this takes ten to fifteen minutes; at moderate rates (500 to 1000 r.p.m.) five to ten minutes; at higher rates (1000 to 2000 r.p.m.) but one or two minutes. The lower speeds were first used in order to avoid hemolysis, but experience has shown that high-speed centrifuging is seldom if ever a factor in the production of hemolysis. An ordinary urine centrifuge is satisfactory. A layer of clear serum forms above the clot, and this serum is easily matched with standards contained in tubes of the same bore. Sealing, centrifuging and determination may be made within the first twenty-four hours after taking the blood. Determination should be made with diffuse daylight. Accurate readings cannot be made with artificial light.

The Standards. The standards are made up of aqueous dilutions of potassium bichromate. Meulengracht's original standard of

Index	2	2 to 10,000	(1 to 5000)
"	4	4 to 10,000	(1 to 2500)
"	6	6 to 10,000	(1 to 1666)
"	10	10 to 10,000	(1 to 1000)
"	15	15 to 10,000	(1 to 666)
"	20	20 to 10,000	(1 to 500)
"	30	30 to 10,000	(1 to 333)
"	50	50 to 10,000	(1 to 200)
"	75	75 to 10,000	(1 to 133)
"	100	100 to 10,000	(1 to 100)

potassium bichromate, 1 to 10,000, has been arbitrarily chosen, according to present usage, to represent an icterus index of 1. The ten standards in 2-mm. tubes, as shown on page 850, are recommended as a satisfactory set.

The standard solutions can easily be prepared as follows: Accurately weigh out 1 gm. of potassium bichromate into a 100 cc. volumetric flask and dilute with distilled water up to the 100 cc. mark. This gives a 1 to 100 dilution or a standard solution of index 100. From this solution all the other dilutions may be prepared very simply. One cubic centimeter of this solution diluted in a volumetric flask to 100 cc. gives a dilution of 1 to 10,000 or a standard solution index 1; 2 cc. diluted up in the same fashion give a dilution of 2 to 10,000 or a standard solution of index 2; 4 cc. similarly diluted to 100 cc. give a standard solution of index 4; 6 cc. give a solution of index 6, and so on for the remaining standard solutions. Tubes of 10-cm. lengths are cut, one end sealed, and the solutions introduced with the aid of a fine capillary pipette. The tubes are filled half way, and the open end sealed in the edge of a flame. In the dark these standards keep indefinitely. After exposure to light over a long period they become slightly paler. This change is very slight.

The following table shows the perceptible color variations of standards in 3-mm. and 2-mm. tubes.

STANDARDS IN 3-MM. TUBES.

Range of indices.	Perceptible differences.
1 to 16	1
16 to 32	2
32 to 48	3
48 to 64	4
64 to 80	5
80 to 96	6
96 to 112	7
112 to 128	8
128 to 144	9

STANDARDS IN 2-MM. TUBES.

Range of indices.	Perceptible differences.
1 to 10	1
10 to 20	2
20 to 30	3
30 to 40	4
40 to 50	5
50 to 60	6
60 to 70	7
70 to 80	8
80 to 90	9

In the range 1 to 16 with 3-mm. standards any two consecutive indices can be differentiated; from 16 to 32, indices differing by 2 can be differentiated; 32 to 48, indices differing by 3, and so forth. The threshold change occurs around 20 with 3-mm. tubes; around

15 with 2-mm. tubes. Because of the nature of the scale, the smaller the icterus index, the easier is its numerical determination, and the higher the index, the smaller the difference between consecutive standards and the more difficult the numerical determination. For example, there is the same difference in color intensity between 100 and 200 as between 1 and 2.

It will be noted that in the range of latent jaundice, indices 1 to 16, the consecutive values of the scale are easily determined by both 2-mm. and 3-mm. tubes. Above 16, exact numerical determinations are of little importance, and the accuracy permitted by the above color differentiations will easily satisfy clinical requirements.

Sources of Error. There are a few sources of error which must be considered.

1. Hemolysis throws off the determination; tubes showing it must be discarded. It seldom occurs if the tubes are carefully cleansed and dried, and if excessive squeezing when taking the blood is avoided.

2. Serum allowed to stand for twenty-four hours or more becomes cloudy and changes color. The determination should be made within the first twenty-four hours.

3. During the periods of food digestion and absorption the blood serum is often cloudy as a result of the presence of food lipoids. Clear serum is essential for accurate readings. This difficulty can be avoided by taking the blood in the fasting state (before breakfast or four to five hours after a meal).

4. Hess and Myers[8] have shown that the color of blood serum may be due to pigments absorbed from the gastrointestinal tract. In infants, after the ingestion of a diet rich in carotin and xanthophyll (carrots, spinach, egg yolk, oranges, and so forth), the color of the serum was found to be considerably deepened. Bernheim,[7] studying adults, did not notice any change in the serum after the ingestion of eggs and oranges. Carrots, however, did deepen the serum. Taking the blood in the fasting state will rule out this source of error.

5. In addition to bilirubin, there are normally other pigments in the blood in very small amounts. These pigments do not appreciably affect the icterus index. The yellow color of the serum in most cases matches closely with the standards. In some cases of intense jaundice, however, the increased presence of these minor pigments may influence the determination. A greenish tinge to the yellow serum in such cases is apt to cause a higher reading. However, this error is not important, and in the lower range of the scale, where a very accurate determination is of value, these secondary pigments do not affect the reading.

Conclusion. 1. A new and very simple clinical method for the determination of the icterus index is presented: a few drops of blood are taken up into a 2-mm. tube, centrifuged, and the serum compared with standards.

2. Venipuncture is obviated by this method and for this reason it is convenient for frequent determinations of the icterus index, and is particularly suitable for the study of the icterus index in children and infants.

3. Experience has shown this test to be accurate and reliable.

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TULAREMIA.

With Report of Eleven Cases.

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Tularemia is one of the few new diseases of man that has been discovered in the past fifteen years, and the only one that has been worked out from the beginning by American investigators. It is an acute infectious disease caused by the Bacterium tularense, and is divided into two types, the glandular and the typhoid type. It is transmitted by blood-sucking insects that bite man and animal and is characterized by marked debilitation. The incubation period is from two to five days (Francis[1 2 3]).

Because of the various observers and the different conditions under which it has been first noted, it has been called by many different names. Thus it was first heard of in 1911, when McCoy[4] described a *plague-like disease of rodents*, because of the death in large numbers of ground squirrels in Tulare County, Calif. Pearse[5] called it *deer-fly fever* because he noted it as a disease of man carried by the blood-sucking deer fly. The name *rabbit fever* was given following an attack that occurred in a man in the market at Washington, D. C., after he had dressed some jackrabbits. Dr. H. C. Lamb, in a paper read before the district medical society of South Idaho in 1923 (unpublished) called it *glandular type of tick fever*,

thinking it was a type of the Rocky Mountain spotted fever. The name *tularemia* was given the disease by Dr. Edward Francis in 1921, since the disease had been connected with the organism that was isolated by McCoy and Chapman,[6] in 1911, from the ground squirrels in Tulare County, Calif, and called Bacterium tularense because of the county in which they first discovered the organism. By this name it is quite generally known at present.

The disease has now been reported from twenty-three states and the District of Columbia, 146 cases in all being on record with positive blood agglutinations (report from Dr. E. Francis, February 20, 1926.)

Its transmission may be by a number of blood-sucking insects. Francis[1] reports experiments performed in its transmission, using blood-sucking deer fly, rabbit louse and bed bug, mouse louse and also in a later publication[1] by the wood tick of the Rockies, the same that transmits Rocky Mountain spotted fever. This is the usual organism for transmission in this part of the country. One may also become infected by briers and burs which have come in contact with infected material and subsequently injured some one through handling. In the laboratory workers there are a number of interesting ways that infection has taken place, from urine, feces and so forth of infected rabbits (Francis[3]). Practically all laboratory workers working with the organism have developed the condition.

Clinical Picture. The disease presents two types, the glandular and the typhoid. In the glandular type there is fever and prostration and a small, reddened area at point of infection, with swollen glands in the region drained by the primary point. The glands quite often go on to suppuration. The typhoid type speaks for itself. The patient has fever of varying degree, lasting over a considerable length of time, and is prostrated and confined to bed for a period of weeks or even months. In both types the effects last over a considerable time, with loss of weight, loss of appetite and strength. The onset is usually sudden and the primary point of infection must be looked for carefully.

The treatment is more or less symptomatic. The glands should not be opened until fluctuation occurs, according to the general consensus of opinion. Rest in bed in the acute stage, and for the loss of appetite and general weakness, following the acute symptoms, I have had good success with a mild tonic, such as elixir of iron, quinin and strychnin. The local ulcer that develops at the point of the primary infection in the glandular type is best treated with warm moist dressings. It may be stated here that in the glandular type there is almost always a primary point of infection whereas in the typhoid type there may be no local lesion at all. The typhoid type has occurred mostly among the laboratory workers.

The following 11 cases were seen by me in Garfield County, Mont., during the summer of 1925. Most of the cases resided at a long distance from Jordan and were seen only a few times, thus rendering it necessary to depend on the patients themselves for the data as to early infection, symptoms, time and source of infection.

Case Reports. CASE I.—Mr. F. C., a rancher, aged forty-five years, was first seen July 8, when he reported because of what he called tick fever, complaining of fever, weakness, tick bites (3 in number on right shin).

The tick bites occurred one after the other in quick succession on the right shin about six weeks previous to reporting. These were swollen, quite painful and later broke down, discharging thin pus, and were covered with a black crust, which when removed showed a dirty necrotic base. Shortly after the tick bites the patient began to have fever, felt ill, weak, lost his appetite, and the glands in the right groin began to enlarge but were not painful. He had not been able to work for the past three weeks on account of weakness.

Physical examination was not remarkable. Temperature, 99.2°; pulse, 80. Patient looked ill. Locally at point of the tick bites were 3 ulcers, about ¼ inch in diameter, the bases dirty and necrotic, the edges raised and reddened, but without lymphangitis. The glands of the right groin were swollen, being about the size of hickory nuts and were not tender. Blood serum sent to the Hygienic Laboratory at Washington was reported positive for Bacterium tularense in dilutions of 1 to 10 to 1 to 40.

Treatment consisted of hot moist dressing to local ulcers, heat to glands of groin and later elixir of iron, quinin and strychnin. The patient was under observation until July 22, when he returned to work much improved, the gland in the groin still swollen, however. He reported about a month later that although he was feeling quite well, the glands will occasionally swell up and then get smaller.

CASE II.—Mrs. H. F., aged thirty-eight years, wife of a rancher living about 9 miles east of town, first reported, July 2, complaining of an ulcer on the dorsal surface of the second finger of each hand and swollen glands in both axillae, also she complained of a tired feeling and a loss of appetite. She gave a history of having pricked her fingers at the site of the ulcers while pulling burs from the wool of a pet sheep. The sheep was apparently in good health at the time and has remained so. At the points of injury a small ulcer developed which did not heal with ordinary means, but seemed to grow gradually worse. With the increase in size and severity of the ulcers, the glands in the axilla gradually enlarged and were slightly tender. With the glandular involvement she began to run a slight fever, and felt tired and worn out, but was not confined to bed. Her appetite also was not as good as it had been and for the past two weeks she had been losing a little in weight.

Physical examination revealed nothing of importance except slightly pale complexion and a temperature of 99° and about six months' pregnancy. Locally on the dorsum of the second finger of each hand there was a rather dirty looking crater-like ulcer, about the size of a split pea. The base was covered with a dirty exudate, the edges were elevated and reddened. The glands in each axilla were enlarged to about the size of hickory nuts but were not markedly tender. Blood serum collected on July 11 was reported positive for Bacterium tularense in dilutions of 1 to 10 to 1 to 320.

The treatment consisted of hot, moist dressing to the ulcerated areas and elixir of iron, quinin and strychnin internally. The patient improved quite rapidly and was confined, November 1.

Case III.—J. N., aged six years, a school boy, living 30 miles west of Jordan, was first seen, July 8, when his mother brought him to the office because of a small ulcer on the scalp, just within the hair line about in the center, also because of swollen glands on each side of the neck just back of the ear. About May 1 the boy began to complain of stiffness of the neck, the swollen glands were not discovered until about one week later. On examination, the ulcer was found in the scalp, being about the size of split pea and covered with a black scab. This was treated by two doctors without any change, and the boy began to act languid and appetite was poor. He had a slight temperature but the exact amount is not known. The parents were worried about his condition and especially about the swollen glands. There is no history of injury or tick bite in the region of the ulcer. The boy had been going to school and there had been a considerable number of dead jackrabbits around the community.

On examination, a small ulcer about ¼ inch in diameter was found slightly to the right of the midline just back of the hair line of the scalp. The ulcer was fairly clean, but the center contained a small point of pus which could not be removed by moderate pressure. The glands behind both ears were swollen but not tender, and there was no fluctuation. The glands varied in size from a bean to a hickory nut, the largest being on the right side. Blood drawn on July 14 was reported to agglutinate Bacterium tularense in dilutions of 1 to 10 to 1 to 320.

Treatment consisted of hot boric dressings to the ulcer and heat to the glands of the neck, as they appeared to be going on to pus formation. The patient was told to report in two weeks, when one of the glands was definitely broken down and was, therefore, incised and a moderate amount of rather clear pus was obtained. The patient was put on syrup of ferrous iodid. Last report was that he was doing very well.

Case IV.—R. McK., aged fourteen years, a school boy, living 30 miles from Jordan, was first reported, July 19, because of soreness and swelling of the second finger of the right hand, and swelling in right epitrochlear and axillary glands. The patient states that he had been feeling rather badly for the past two weeks, running a little fever, felt worn out, languid and no appetite. He had not noted the sore finger until the past four or five days when the glands also made their appearance. He had not had any other open sores on his hand and does not remember having injured the finger in any way. He had been with a band of sheep since leaving school, but there did not seem to be any sickness or tick paralysis among them, but there had been a number of dead jackrabbits in the vicinity and he had handled a few of them, all of which seemed to be infested with ticks.

On examination, the second finger of the right hand was swollen and slightly tender, tenderness extending down to the palm of the hand and some tenderness on flexion of the finger. The glands of the right epitrochlear and axillary region were swollen and slightly tender. Temperature, 100°; white blood cells, 14,300.

The finger was opened quite widely and a through-and-through drain inserted as a tendon sheath infection was suspected; hot applications were applied to the glands of the elbow and axilla. The finger improved and the glands decreased in size but the patient complained of continued loss of appetite, tired, worn-out feeling and loss of weight; it was not until this time that tularemia was suspected and a sample of blood drawn and the serum sent to Washington where it was reported positive for Bacterium tularense in dilutions of 1 to 10 to 1 to 1280. Following this the patient was given elixir of iron, quinin and strychnin with quite satisfactory general improvement.

CASE V.—Mrs. G., aged forty years, wife of a rancher, living about 20 miles west of Jordan, reported, August 8, because of large swelling in right axilla. Patient states this began to develop about a week following the removal of a small brier from between the thumb and the index finger of the right hand, about six weeks before reporting. She had stuck the brier in her hand while working in the garden; her husband had removed it but an ulcer had developed at the site of injury, which was very chronic and healed in about five weeks. She also had a slight temperature, loss of appetite and strength. The swelling in the axilla had been gradually developing since the appearance of the ulcer, but had not been tender.

On examination, there was nothing of importance except the abscess in the right axilla which was about the size of a walnut, very soft and the skin over it was bluish-red in color. At the site of injury there remained a scar, but no open sore. The treatment was merely to open the abscess, from which about an ounce of greenish pus was obtained, a drain was inserted and hot packs applied. The patient was given internal medication of elixir of iron, quinin and strychnin. Blood collected and serum sent to Washington, which was reported as positive for Bacterium tularense in dilutions of 1 to 10 to 1 to 640. Later reports from patient were continuous improvement.

CASE VI.—J. W. M., aged forty-two years, a sheep herder, reported, August 27, because of an indolent ulcer on the dorsum of the right thumb and numerous small hard swellings over the dorsal surface of both hands. The illness began about three weeks before, when he first noticed the ulcer; this did not heal, but seemed to grow gradually larger, and during the past week the small nodules had developed on the hands. He had also noticed some red streaks extending up the arm from the ulcers. The patient stated that he had been bitten by ticks on several occasions, but not in the area of the ulcer, but he had been handling sheep a good deal during the summer and there were a number of ticks on them.

On examination, there was an ulcer about $\frac{1}{4}$ inch in diameter on the dorsal surface of the right thumb with slight lymphangitis extending up the arm. The ulcer showed a moderately clean base with slightly reddened and swollen tissue around the edges. Over the backs of the hands were small swellings about the size of a grain of rice, quite hard with reddened tops. The glands in the right axilla were slightly swollen and tender. Temperature, normal; white blood cells, 11,000; red blood cells, 4,800,000. Differential count showed a slight increase in lymphocytes. Blood serum reported to agglutinate Bacterium tularense in dilutions of 1 to 10 to 1 to 640. Both hands improved with hot boric dressings. The patient was given elixir of iron, quinin and strychnin internally with improvement.

CASE VII.—F. C., aged nine years, a school boy, living 30 miles west of Jordan, was first seen, July 27, when he was brought in because of high fever and delirium. The boy had been ill for the past three days, complaining mostly of fever. He had not complained of any pain or soreness, and during the past two days he had been delirious at times. There was no cause for the condition that could be elicited from the mother, but on examination, aside from a temperature of 103° with delirium, was found a small, reddened spot on the dorsum of the left foot and some swelling of the glands of the left groin, which caused the patient to flinch when pressed. The sore spot on the foot was ascribed to the shoe rubbing at this spot, and the mother remembered that he complained of this spot before he took sick. On questioning it was found that the boy had been going barefooted a good deal and, although he did not remember hurting the foot, there was a good chance for an injury to have taken place at this spot.

The temperature continued to run quite high for a week, ranging from 102° to 104°, with delirium when it was at its peak. Tularemia was suspected, but because it was so early in the disease I did not expect to have a positive report on blood collected at this time, but, nevertheless, a specimen was collected and sent to Washington and was reported negative. Because of the high fever without anything very definite to account for it, a lumbar puncture was done; the fluid was normal. White blood cells were 17,000, with an increase of polymorphonuclears. The foot and groin were treated with hot dressings and the inflamed area of the foot opened to permit drainage. The boy improved and was allowed to go home in ten days, but told to report in two or three weeks for another sample of blood. The second sample which was not drawn until September 3 was reported positive for Bacterium tularense in dilutions of 1 to 10 to 1 to 1280. The boy had continued to improve, but carried a slightly elevated temperature for about six weeks. He was put on internal medication of syrup of ferrous iodid, and the last report was that he was practically back to normal.

CASE VIII.—Mrs. J. B. K., a housewife, Jordan, P. O. first reported, August 11, because of an ulcer on the dorsal surface of the little finger of the left hand, swelling in the left axilla and a worn-out feeling. The patient came from Spokane, Wash., about June 15, and was feeling well at that time. About July 15 she noted a small, reddened area on the dorsum of the little finger, and it had the appearance of having a sliver in in the center of it. She did not remember having injured it in any way. During the next few days she began to run a fever and had what she called an attack of influenza, from which she has not entirely recovered. In questioning the patient, it was found that she had dressed a jackrabbit for the dogs a few days previous to taking ill. (A number of dead jackrabbits had been seen around the vicinity.)

On examination, a small ulcer was found on the dorsum of the little finger of the left hand; this was about ⅛ inch in diameter, and presented a reddened raised edge with a base covered with dirty exudate of grayish color. The glands of the left axilla were enlarged to about the size of hickory nuts. Hot dressings were applied to the finger and hot packs to the axilla. The patient was told to report later to have axillary glands opened. This was done, October 1, when about an ounce of greenish liquid pus was obtained. There was no odor to the pus or the later dressings.

Blood collected on September 12 was reported positive for Bacterium tularense in dilutions of 1 to 10 to 1 to 640.

The patient left for Minnesota shortly after the glands were opened, but was considerably improved by that time.

CASES IX, X and XI.—These 3 cases are taken together because of the similarity of their conditions. They were 3 brothers, aged six, seven and nine years. The mother brought the youngest lad to see me, October 23, because of an infection on the dorsum of both hands, swelling in the axilla and what she said was failure to recover from an attack of "flu." At this time I obtained the history of the 3 brothers having dressed a jackrabbit about three weeks previously, and shortly after this the 3 of them began to show signs of not feeling well, acted tired, worn out and had no appetite. Also she noticed several small areas of infection on the dorsum of the hands, which appeared as small boils, and later they complained of soreness in the axilla, which on being examined showed a few swollen glands. Hot boric dressings were applied to the infected areas and the mother told to report in about two weeks and bring the other 2 brothers.

At the time of the second reporting all 3 lads presented small sores

on the dorsal surface of both hands with swollen glands in the axilla. Blood was drawn at this time from only 1 of the boys, as the mother had objected to having it taken from the other 2 after the first one had cried some. But owing to the similarity of the infection, it was thought that if this was reported positive that the other 2 must be the same. This was sent to Washington and was reported positive for Bacterium tularense in dilutions of 1 to 10 to 1 to 640, thus making the diagnosis of tularemia in this case. The usual treatment was carried out and syrup of ferrous iodid given internally. There has been no report from these since.

This is a rather interesting group of cases because the infection must have taken place through the handling of the rabbit. Rabbits are supposed to die in ten days after becoming infected, and as it was too late for ticks, the rabbits must have been infected from some other means, perhaps the rabbit louse. If this be the case the disease would be expected to run through the winter months.

No special precautions were taken in treating or caring for any of these cases and no secondary infection occurred.

Of course this is too small a group of cases to draw any conclusions of value concerning the disease, but it may add to the data already collected concerning it. Dr. Francis has given a quite complete study of the condition both in the laboratory and clinically in his article on tularemia.[3]

Conclusions. 1. Tularemia is a recognized disease in the United States.

2. The common type met with in practice is the glandular type, showing, however, a varying degree of systemic reaction.

3. It is remarkable for its debilitating effect and its chronicity.

4. The site of infection is quite similar in all cases.

5. Glands may either break down or gradually disappear.

6. Treatment is symptomatic.

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THE EFFECT OF EMOTION ON CERTAIN CASES OF ASTHMA.

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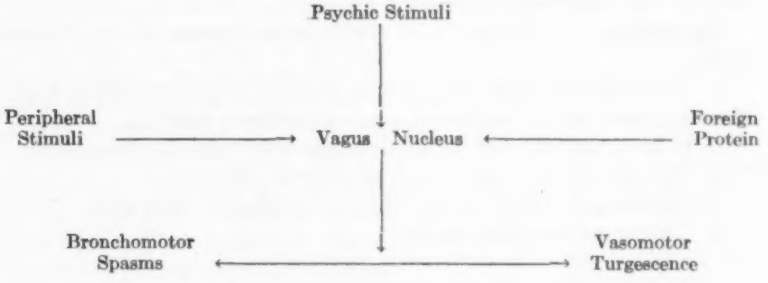
Neurotic factors have frequently been noted among certain cases of bronchial asthma. These factors have been very difficult to describe or define. Some psychiatrists[1, 2] have said that selected cases of asthma are fixation hysteria in which emotional storms affect the bronchi markedly. Déjérine and Gauckler[3] have spoken of such cases as pseudoasthma. Oppenheim[4] goes so far as to say that most cases of asthma represent some kind of neurosis. W. Langdon Brown[5] presents an interesting diagram which gives his comprehensive "formula for asthma" as follows:



Graham Brown[6] reports a case of bronchial asthma that developed after prolonged fear. He offers the theory that fear exhausted the adrenals[7] and left the patient with a marked vagotonia,[8] which vague syndrome seems to be present in many asthmatics. He also noted asthma in association with various psychic stimuli, especially mental depression. Although Walker[9] admits that asthma is associated with neurotic tendencies in some cases, he does not include it in his etiologic classification of bronchial asthma. After observing a number of cases of bronchial asthma, similar to those with the following histories, the writers became interested in the effect of emotions on the respiration and circulation of such patients.

Case Reports. Case I.—A married man, aged thirty years, a farm laborer, with fair industrial history, had always been well until he had mumps during the late war while on an army transport *en route* to France. Upon recovering from mumps he became very ill with influenza and was

in a hospital in France five or six weeks. Following this, he had bronchitis but was able to carry on. On one occasion, he thought he was slightly gassed. After the Armistice, upon returning to the United States, he was more restless, and noted a gradually increasing shortness of breath, especially when economic conditions forced him to engage in hard manual labor. After a discouraging period of this type of work he suddenly developed an attack of asthma and soon thereafter was hospitalized (September). Aside from some loss of flesh and typical asthmatic breathing, he presented sibilant râles throughout the chest and marked immobility of the diaphragm. Much mucopus was expectorated, which by numerous examinations was found to be free from tubercle bacilli. Roentgen ray of chest showed chiefly the immobility of the diaphragm and some hilus thickening. Under care and cheerful surroundings the patient improved rapidly. The diaphragm became mobile; he gained in weight, and was able to be up and about without distress. It is of interest to note that one day, shortly before he left the hospital, he received some unpleasant news and almost at once developed a marked asthmatic attack, from which he recovered in a few days. Sensitization tests by the usual series of proteins were all negative.

Case II.—A married woman, aged forty-four years, whose father had had asthma, began to have two or three attacks of asthma each year from the age of ten. At sixteen years of age she began to have asthma very continuously and hay fever as well. She sought medical aid all over the country. She was always nervous and domineering and rather jealous. Because of her fretfulness she had been given large doses of bromides and came to the hospital in a marked bromide delirium, from which she recovered in a few days. During the delirium she showed no signs of asthma; on the contrary, she talked excessively and screamed with facility. She felt persecuted and guilty and begged to be spared from punishment. Upon recovery from the delirium she was emotionally unstable and irritable, showing only occasional slight attacks of asthma at first; later, however, these became marked and were invariably initiated by sobbing over intimate personal matters that were disagreeable to her. The sobbing would blend, in the course of fifteen minutes, into an asthmatic attack of marked degree. Sputum examinations were negative for tubercle bacilli. Roentgen ray of the lungs showed some evidence of old quiescent tuberculosis. Sensitization tests of the skin were slightly positive for many proteins.

Case III.—A married woman, aged thirty-one years, began to have asthmatic attacks at the age of seven years, initiated by an outburst of temper. She had always been nervous and irritable. Attacks have come and gone and she has lived in dread of them. She is unhappily married. Quarrels with her husband frequently end with an asthmatic attack. She was brought to the hospital in a state of marked anxiety and depression, during which time she was relatively free from asthma. As these mental symptoms subsided she again began to have asthmatic attacks. Sensitization tests were not done, but no history of sensitization to proteins or pollens could be elicited.

Case IV.—A married man, aged forty-two years, an insurance salesman, came to the hospital in a marked depression over financial affairs and quite anxious about his condition. He came of a family in which there was mental disease. He had had a nervous breakdown at the age of eighteen years, accompanied by asthma, which caused him to come from Wisconsin to Colorado on account of his health. He had had no asthma in the mean time until he became depressed several months before admission to the

hospital in November, 1925. Upon recovery from his depression his asthma left him entirely. His physical examination was essentially negative aside from being slightly underweight. Skin sensitization tests were not done; no history of protein sensitization could be elicited.

CASE V.—A single man, aged forty-six years, a male nurse, had always shown some inadequacy and was of a roving disposition. He had always been well until at the age of forty years he became depressed and worried, following which he developed marked bronchial asthma. The attack began in July and lasted eight months. He came from Indiana to Colorado on account of his health; recovered and remained in Colorado. At the age of forty-five years he again had a period of discouragement, followed by an attack of asthma lasting two months. This attack began in March. The attacks were preceded each time by a feeling of depression and discouragement and a "pain pressure" under the sternum. Roentgen ray and physical examination of the lungs gave no evidence of active pulmonary tuberculosis. His pupils were inactive to light and was unequal. He had marked dental sepsis. His blood and spinal-fluid serology was negative. Skin tests were not done, but no history of sensitization to protein was elicited.

CASE VI.—A school girl, aged fourteen years, became very jealous of her stepfather, and developed a psychosis in which she was impulsive at times. She would not talk and was seclusive. She made much of some autistic love affairs. When she began to recover from her psychosis she had a marked attack of bronchial asthma which lasted several weeks. Skin sensitization tests were not done, but no history of protein sensitization could be elicited.

Two groups of patients were studied. One group consisted of 3 asthmatic patients in whom asthma was apparently due entirely to protein sensitization. These were used as controls. The second group consisted of 6 patients who from their history appeared to develop asthmatic attacks in connection with emotions. These were patients who had had at one time or another a definite neurosis or psychosis.

The method employed was to use the ordinary electrocardiographic "hookup," as shown in Fig. 1, and additional tracings of the respiratory movements were obtained by means of a pneumograph, placed about the patient's thorax and connected to a tambour. The writing point of the tambour was then placed parallel to the shadow of the string of the electrocardiograph used in the ordinary manner. All patients were free from asthmatic attacks at the time the experiments were performed.

The following procedure was used on all subjects. The first tracings were taken with the patient normally at rest. The patient was next instructed to think about something which was known from his history to be emotion-producing. During this period of meditation the second series of pulse and respiratory tracings were taken. After completing this tracing the patient was instructed to relax and rest as much as possible. During the rest, and ten minutes after the introduction of the emotional stimulation,

the last, or third, series of tracings was recorded. Thus a period of emotional stimulation was placed between two control periods of rest.

From such studies it became apparent that the patients whose asthma was explained on an allergic basis gave very little emotional response, as demonstrated in the respiratory curves or the pulse rate; while the asthma apparently on an emotional basis gave fairly constant emotional responses both in the respiratory curves and pulse rates. Charts I and II summarize these findings. The expiratory phase of respiration, which is usually markedly prolonged in asthma, was especially studied and under emotional stress this became definitely lengthened in the psychopathic group. Other

FIG. 1.—*X* indicates tambour connected with pneumograph about the patient's chest. The writing point of the tambour is placed parallel to the shadow of the string of the electrocardiograph.

manifestations in the psychopathic group were purposeless movments and fine tremors during emotional stimulation, such as have been previously described.[10]

In the psychopathic group emotions produced no change in the character of the electrocardiograms in any lead; but the pulse rate during the whole experimental period was rapid, being slightly more so during the period of emotional stimulation.

Fig. 2 presents the electrocardiographic and respiratory curves of a patient whose asthma was associated with emotional upsets. The stimulation period shows very marked alterations in the respiratory curve. The respiratory rate was not increased, but the amplitude and regularity of the respiratory curve was markedly altered by the

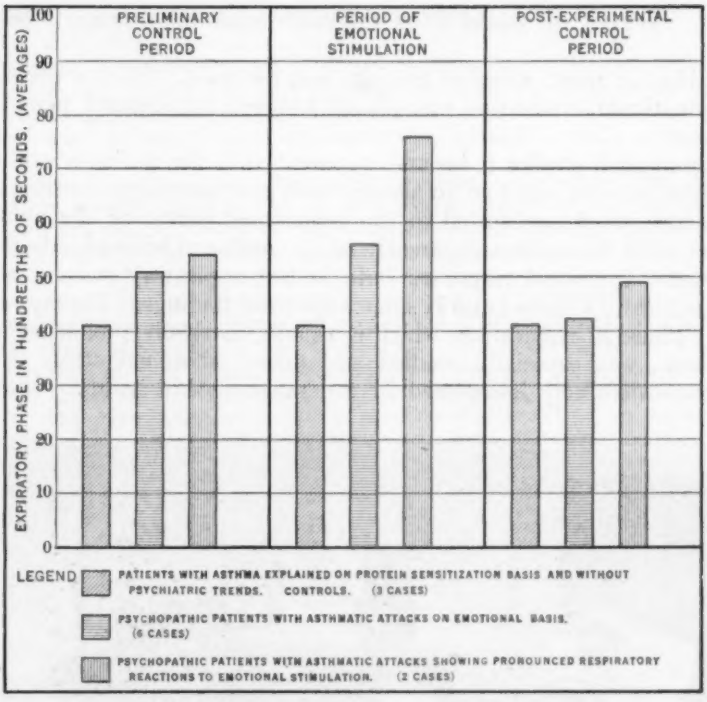


CHART I.—Length of expiratory phase of respiration.

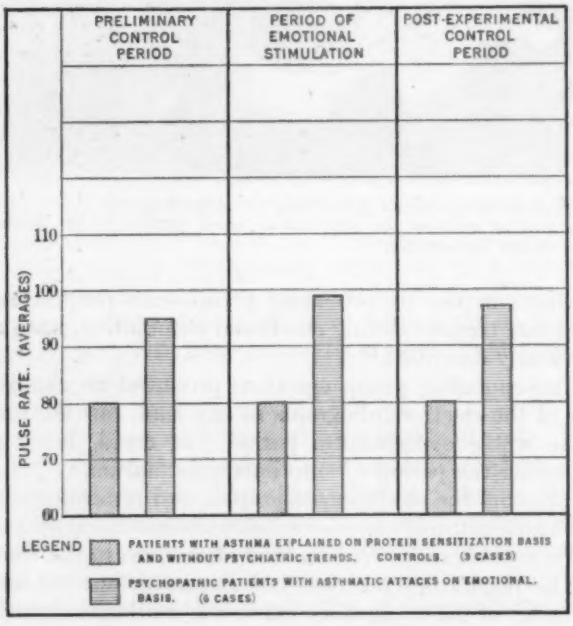


CHART II.—Pulse rate.

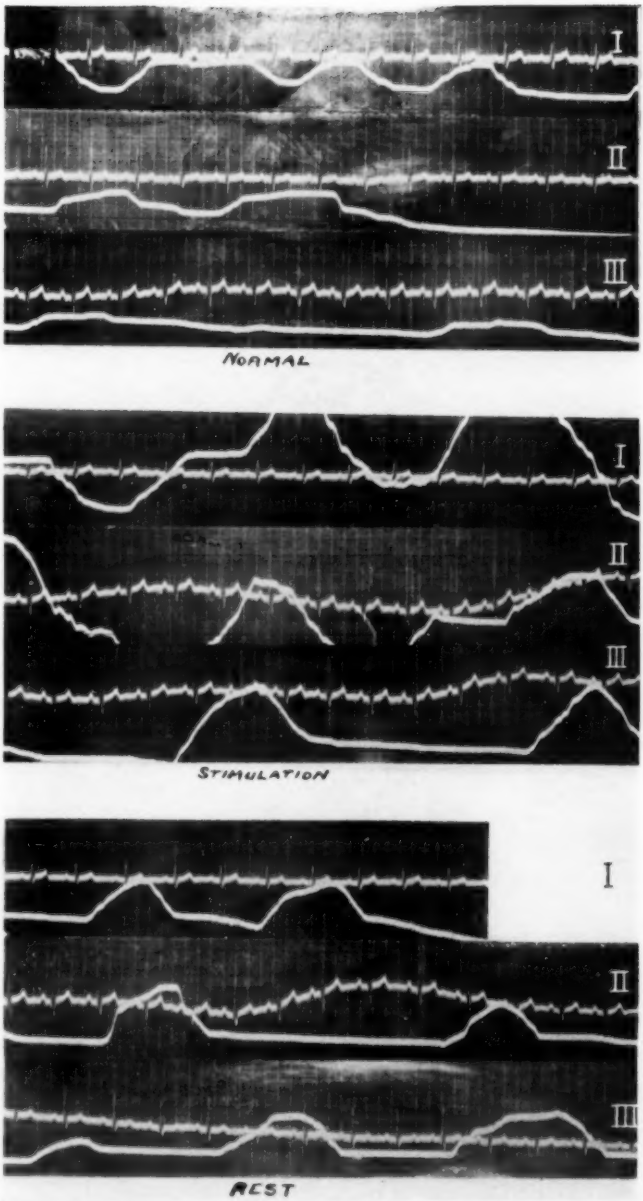


FIG. 2.—Electrocardiographic and respiratory curves from a patient with bronchial asthma apparently on an emotional basis. The group of curves in the center were taken while the patient was subjected to emotional stimulation. The curves at the top (normal) and at the bottom (rest) represent control periods.

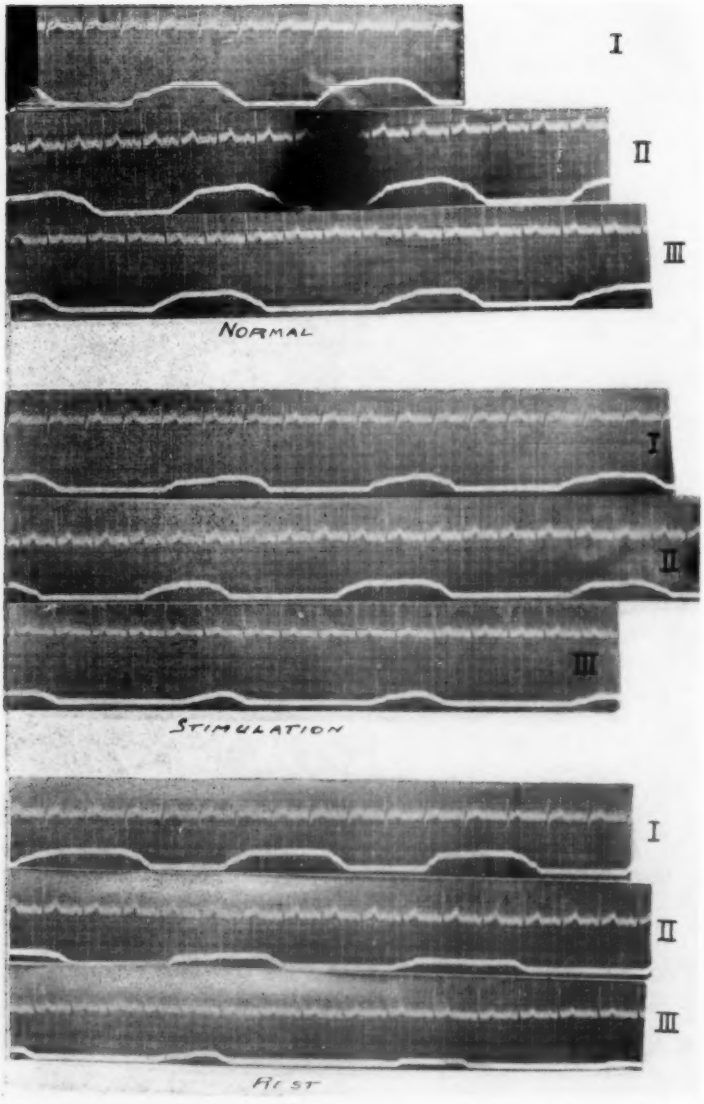


FIG. 3.—Electrocardiographic and respiratory curves from a patient with bronchial asthma on a protein-sensitization basis. The group of curves in the center were taken while the patient was subjected to emotional stimulation. The curves at the top (normal) and at the bottom (rest) represent control periods.

stimulation. Fig. 3 presents similar curves for an asthmatic, definitely sensitive to protein, whose electrocardiographic tracing and respiratory curve plainly did not show response to emotional stimulation.

Such studies tend to delimit a small group of patients in whom mild, or even severe, attacks of asthma seem to be related to psychic stimuli (emotions usually). It is quite possible that two or more of the etiologic agents so ingeniously presented by the "asthma formula" of W. Langdon Brown may be effectual in producing bronchial asthma. It would seem important to study very carefully all cases of asthma not explained on a protein sensitization basis, in order to determine the pharmacodynamic effect of psychic stimuli.

Summary. 1. Emotions, or psychic stimuli, seem to induce bronchial asthma in a limited number of people without a history of protein sensitivity.

2. Patients with a history of asthma associated with psychic stimuli were studied while under the influence of emotion. They demonstrated considerable alteration in the amplitude and regularity of the respiratory curves but little or no changes in rate. The expiratory phase was lengthened and a slight increase in pulse rate was noted. Patients whose asthma was explained on a protein sensitization basis showed no such changes.

3. In the absence of protein sensitization, or a history of the same, a careful study of the relation between emotions and asthmatic attacks is indicated and should help to explain the disease in a limited number of patients.

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MONGOLIAN IDIOCY IN TWINS.

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and

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There are a number of recorded cases of Mongolism in twins. These reports are of interest and of some significance in relation to the etiology of Mongolian idiocy. In passing it may be remarked that in future reports it would be well for authors, in addition to simply noting that they had observed such an occurrence, to give a description of the patients and also to present illustrations of them. In this way, there will be less strain put upon the credulity of the sceptically-minded. A satisfactory description is given in only 7 of the 24 cases collected in this paper and an illustration accompanies only 5 of them.

A number of theories have been advanced in explanation of the cause of Mongolian idiocy. Many of these are based on the idea that the etiologic factor is operative during pregnancy and it has been thought that illness or nervous strain during that period has had some influence upon the developing fetus. Syphilis, alcoholism, tuberculosis and consanguinity have also been considered as causes but the importance of these has not been borne out by careful study. The term "sexual exhaustion products" has been applied to Mongolians because of the statistical evidence brought forward to indicate that they often occurred at the end of a number of pregnancies or as the first and only child of elderly primipara. Such a sequence of events does not happen consistently enough, however, to have great significance and, moreover, it has been shown that two or more Mongols may occur in the same family and generation. The condition has also been considered to be a reversion to a more primitive type, a view which has been recently championed by Herrman[19] who believes that such factors as consanguinity, advanced age of the parents and the like serve to bring to light latent recessive characteristics.

In any event, analysis of the data in the present report helps to refute the theories which would hold that causes operative during pregnancy are at fault and supports the belief that the cause lies in a defect in the germ plasm. Taking for granted that all the reported cases are authentic and considering first those given in Tables I and II, it is seen that in these 15 cases the sex of the Mongol was always different from that of the normal twin, thus

proving that they were the result of double ovum pregnancies. In the 3 cases (Table III) in which Mongolism occurred in both twins the sex was identical. In these the twins could have been either monozygotic or dizygotic with a strong presumption in favor of the fact that they were the former. Halbertsma[15] points out that in order to consider them the result of a two-egg pregnancy it would be necessary to allow for the coincidence of two separate ova both doomed to Mongolian idiocy being fertilized at the same time. Nevertheless, it is unfortunate that the condition of the placenta is not known in these cases. In the 6 cases (Table IV) in which Mongolism occurred in 1 of twins of the same sex it is noted in 4 that there were 2 placentas; in the other 2 the history in relation to the placenta is not given.

TABLE I.—MONGOLIAN IDIOCY IN ONE OF TWINS OF DIFFERENT SEX.

Names of authors.	Sex of Mongol.	Sex of normal twin.	Satisfactory description	Photograph of Mongol.	Photograph of twin.	Remarks.
Neumann	M.	F.	No	No	No	
Haltgren	M.	F.	No	No	No	
Cassel	M.	F.	No	No	No	
Cassel	F.	M.	No	No	No	
Swanberg and Haynes	M.	F.	Yes	Yes	No	
McLean	M.	F.	Yes	Yes	Yes	
Halbertsma	M.	F.	No	No	No	
Halbertsma	M.	F.	No	No	No	
Wood	F.	M.	No	No	No	
Shuttleworth	F.	M.	No	No	No	Probably same case as Wood's
Comby	F.	M.	Yes	No	No	
Vas	F.	M.	No	No	No	

TABLE II.—MONGOLIAN IDIOCY IN TWINS OF UNKNOWN SEX.

Names of authors.	Sex of Mongol.	Sex of normal twin.	Satisfactory description.	Photograph of Mongol.	Photograph of twin.
Fraser and Mitchell	?	?	No	No	No
McKee	?	?	No	No	No
Weigall	?	?	No	No	No
Halbertsma	M.	?	No	No	No

TABLE III.—MONGOLIAN IDIOCY IN BOTH TWINS.

Names of authors.	Sex of twins.	Satisfactory description.	Photograph.	Number of placentas.
Hjorth	Same	No	No	?
Strauch	M.	Yes	No	?
De Bruin	M.	Yes	No	?

TABLE IV.—MONGOLIAN IDIOCY IN ONE OF TWINS OF IDENTICAL SEX.

Names of authors.	Sex.	Satisfactory description.	Photograph of Mongol.	Photograph of twin.	Number of placentas.
Clay	M.	Yes	Yes	Yes	?
Halbertsma	M.	Yes (?)	No	No	2
Deitrich and Berkley	M.	Yes	No	No	?
Mitchell and Downing	M.	Yes	Yes	Yes	2
Halbertsma	F.	No	No	No	2
Deitrich and Berkley	F.	Yes	No	No	2

Summary of Reported Cases. Frazer and Mitchell[1] in some notes on 54 cases of Mongolism mention that they have seen 1 instance in which the idiot was one of twins. There is no further description, and the sex of the twins is not mentioned nor is a photograph shown.

Neumann[2] records a case in which the Mongolian twin was a boy and the normal one a girl. Description and details are not given and there is no photograph.

De Bruin[3] reports a case of Mongolism in a boy of two and a half-years of age who was suffering from splenic anemia and catalepsy. His twin brother, it was said, had also been a Mongolian, but had died some time previously and apparently had never been seen by De Bruin. The description of the patient is that of a typical Mongol although no photograph is shown. No note is made concerning the condition of the placenta at the birth of the twins.

Hjorth[4] reports Mongolism in both twins according to Halbertsma (*loc. cit.*). These twins were of the same sex.

McKee[5] reports a Mongolian idiot in one of twins. The sex of the twins is not stated and there is no description or photograph. Personal communication with Dr. McKee brought no further information about this particular case.

Jeffreys Wood[6] reports a case of a Mongolian girl, the twin brother being normal. There is no description or photograph.

Comby[7] describes in detail a Mongolian girl, aged six years, the other twin, a boy, being normal. There is no photograph.

Shuttleworth[8] in a paper on Mongolism mentions the case of a Mongolian girl whose twin brother was normal. At the meeting at which the paper was read Shuttleworth showed a photograph of the two children although this is not to be found in his published paper. This particular case of Mongolism in one of twins seems to be the same as the one reported by Jeffreys Wood and is mentioned in Shuttleworth's presentation through the courtesy of Dr. Wood.

Weigall[9] has seen a twin, aged eight months, with Mongolism,

the other twin being normal. The sex of the twins is not stated and there is no description or photograph.

Hultgren[10] notes in a table in his paper the case of a Mongolian boy whose twin sister was normal. There is no description or photograph.

Cassel[11] in a paper on Mongolism states that he has twice seen a Mongolian twin, once a boy and once a girl. In both cases the other and normal twin was of the opposite sex. No photographs are shown and there is no further description of the patients.

Swanberg and Haynes[12] report in detail a Mongolian boy whose twin sister was normal. There is a photograph of the Mongol but not of the twin.

Clay[13] describes in detail Mongolism in one of twins, both of them boys. He presents a photograph of both twins. It was not known whether these twins were monozygotic or dizygotic.

McLean[14] reports the case of a Mongolian boy whose twin sister was normal. There is description of the children and photographs of both are given.

Halbertsma[15] reports the following cases of Mongolism in twins: (1) One of twin boys ten months of age. Two placentas were present at birth and each twin had its own chorion and amnion. A brief description of the Mongol is given, but the twin is not described except to say it was normal. There is no photograph.

2. One of twin girls four and a half months of age. There were two well separated placentas with two chorions and two amnions. The author simply states that the Mongol was typical. There is no photograph.

3. This case was apparently not seen by the author but it and the following 2 cases were reported by him through the courtesy of Dr. W. M. van der Scheer. The patient was a Mongolian boy whose twin sister was normal. The age was two and a half years. There is no description except to say that the Mongol had club feet. There is no photograph.

4. A Mongolian boy of two and a half years whose twin sister was normal. There is no description or photograph.

5. This, to say the least, is a rather peculiar case in which it was said that the mother had a miscarriage at the end of the third month of pregnancy. Six months later a Mongolian boy was born. There is no description or photograph.

Strauch[16] reports Mongolism in both of twin boys. There is a good description of both patients but no photograph. No statement is made concerning the placenta.

Vas[17] reports a Mongolian girl whose twin brother was normal. There is no description or photograph.

Dietrich and Berkley[18] record 2 cases of Mongolism in one of twins. In the first case, the patient was a male and the twin, also a male, was examined and found to be normal. There is a satis-

factory description of this patient but no photograph is shown. In the second case, a female Mongol is briefly described and the twin sister was said to be normal although she was not seen by the authors. A note is made in the latter case that there was a double placenta. No photograph is shown.

FIG. 1

FIG. 2

Case Report. To the cases already reported, we are able to add another in which Mongolism occurred in one of twins whose sex

was identical. The father and mother of the patient were living and well, the former being thirty years of age and the latter, twenty-seven. One sister of the patient, whose age was five years, was living and well and had no characteristics of Mongolism. The mother had had no miscarriages and there was no history suggestive of syphilis. The birth of the twins was uneventful. Two placentas and two complete membranes were present. The patient, a boy, was first seen by one of us (H. F. D.) when he was two months of age, at which time the Mongolian *facies* was quite evident. The twin brother was not a Mongol and continued to develop normally both physically and mentally. A picture of the twins taken at the age of one year shows the differences in the appearance of the two babies (Fig. 1). A second picture of the patient, taken a month later demonstrates the typical Mongolian *facies* and the rather spade-like hand with a tendency to trident separation of the fingers (Fig. 2). At fourteen months of age, the patient died of laryngeal diphtheria. The somewhat slanting and narrow palpebral fissures; the well developed inner epicanthic folds; the wide space between the eyes; the small mouth with protruding tongue; the spadelike trident hand and the brachycephalic head may all be seen in the illustrations. No cardiac abnormalities could be made out on physical examination. The little finger was not noticeably short or incurved. The tongue was dry and fissured, the anterior fontanelle was still widely open at fourteen months of age and the patient at that time had only three teeth.*

Summary. Including the present case, there have been 24 instances of Mongolism reported in twins. In 15 of these the condition was present in only one of the children, the other and normal twin being of the opposite sex in 11 cases—the sex not being stated in the remaining 4. In 3 cases Mongolism occurred in both twins, the sex being identical. In 6 cases Mongolism occurred in one of twins of the same sex, in 4 of which there were two placentas present at birth, in the other 2 the condition of the placenta was not stated. These facts are in favor of the theory of Mongolism being a germ plasm defect and are against any theory which holds that causes operative during pregnancy are at fault.

In no case has it been demonstrated that Mongolism can occur in one of twins, the result of a single-ovum pregnancy. If such a condition of affairs could be shown to exist it would be against the theory of germ plasm defect even though it would not prove any theory dependent upon the assumption that the etiologic factor is operative during pregnancy.

* We wish to thank Dr. Frank H. Lamb for his courtesy in allowing us to report this case.

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THE ETIOPATHOLOGY OF MYOCLONUS EPILEPSY.

With A Report of Four Cases.

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Myoclonus epilepsy is a true association disease of largely familial incidence, in which the components show some departures from typical epilepsy and typical myoclonus. Until the author recognized its autonomy as an association disease in 1902, it was known as Unverricht's syndrome and the leading systematic writers on the latter were Unverricht himself—whose first study appeared in 1891—and Lundborg, beginning in 1897. The latter in addition to an exhaustive summary of the symptomatology was especially concerned with the family histories and the degenerative heredity of the affected families.

While the disease is rare, its literature is by no means small; but as it is notoriously incurable the chief interest is attached to the predisposition—the extreme disorganization of the motor functions of the nervous system which makes such as affection possible. It is evident that such a striking association of ordinary epileptic seizures with the persistent clonic contractions should have attracted attention long before the recognition of the Unverricht syndrome, but while authors speak vaguely of such an association, individual

cases were not mentioned up to 1868 at least, when Hammond alludes briefly to a possible victim. Oddly enough a much better description of a case was given in 1871 by Gaboriau, the novelist.[1] When it is borne in mind that the condition of simple myoclonus was not isolated until 1881, when Friedrich described it under the name of paramyoclonus multiplex, it is not surprising that a period of latency must have ensued before Unverricht's syndrome could be more generally visualized.

Since the work of Lundborg our knowledge of the disease has not shown much progress. As is natural, atypical cases have been reported and also familial affections which show some affiliation with myoclonus epilepsy, such as the so-called nystagmus myoclonus which may shade into it, while in this connection there is a tendency to postulate a group disease ample enough to comprise association myoclonus with degenerative chorea. Among atypical cases are some in which a familial tendency as well as degenerative heredity are absent altogether but this paradox need not surprise us for it is encountered in all familial disease.

Does the hereditary-degenerative predisposition of the association disease differ at all from that of ordinary degenerative epilepsy which is often enough the sole causal factor of that disease? The genealogical tables of Lundborg appear to show more cumulation in association-disease families—a large number of cases, more cumula-

[1] The description given is as fairly accurate of this affection as was that of the "Alexandrine phenomena" in a novel by Goncourt (cited by Féré), and the embodiment of infantile cerebral palsy in a painting by Ribera (1588–1656) in the Louvre, which bears the title "Le Pied-Bôt." The scene of Gaboriau's novel, entitled "In Peril of His Life," was laid in June, 1871. The villain was the illegitimate son of a feebleminded mother, who herself possessed many mental and physical stigmata of degeneracy. The son, whose name was Cocoleu, was a feebleminded myoclonic epileptic, as evidenced by the romancer's description, doubtless taken from life, and he also possessed multiple stigmata of degeneration. After a life of vagabondage, at 18 he committed arson and homicidal assault without adequate provocation. Yet with quite characteristic modern justice this irresponsible degenerate was sentenced to imprisonment with hard labor for life. Some of the passages of the translated novel bearing especially on the disease picture are as follows:

"He was an idiot and a person more or less defective mentally and physically, besides being subject to a terrible nervous affection which at times shook the whole body and disfigured the face by the violence of uncontrollable convulsions. He was not a deaf mute, but could only stammer out with intense difficulty a few disjointed syllables. Sometimes the country people would say to him: 'Tell us your name and you shall have a sou.' Then it took him five minutes' hard work to utter amid a thousand painful contractions the name of his mother: 'Co-co-co-lette.'"

"It was well that the court used kind words, for Cocoleu was thoroughly terrified and was trembling violently in all his limbs."

"Did Cocoleu follow him? His distorted features betrayed nothing going on within him."

"Big drops of perspiration rolled slowly down his temples and nervous shocks agitated his limbs and convulsed his features" (myoclonus). "But the efforts which the unfortunate man had made during the last hour had exhausted his little strength. He broke into stupid laughter; and almost instantly one of his fearful nervous attacks overcame him: he fell with a scream and had to be carried away" (epilepsy).

tion in brothers and sisters and possibly more direct parental transmission. At the same time we find the same "equivalents" in both strains—idiocy and the milder mental defects, insanity, motor troubles (tics, chorea), migraine, the racial poisons of tuberculosis; alcoholism, etc., and moral delinquencies. In the brothers and sisters of the subjects of association disease we find over and over again simple epilepsy, convulsive tic, insanity and mental defect and in some of these broods a perfectly sound nervous system is quite exceptional. Probably a fundamental difference between the strains producing simple epilepsy and association disease is more cumulation of motor neuroses in the latter, which is just what one would expect from the presence of the myoclonic component. A second differential point may be a greater absence of hysteria in the association disease, which is puzzling when we bear in mind that hysteria often occurs in degenerative strains.

As to the presence of stigmata of degeneration, whether somatic or psychic, there seems to be no difference in the two strains. The fact that there was a certain amount of consanguineous marriage in Lundborg's families is probably without significance for such a degree of inbreeding is common in all small, isolated communities. It must be kept in mind that mere coincidence of epilepsy in some one of its forms with myoclonic spasms at some time in the life of an individual is something quite apart from the association disease for in the latter the two components are blended in a certain way to be considered later. It is even possible that an epileptic may suffer from simple myoclonus or that a subject with the latter might for some reason develop epilepsy, yet the two processes may represent a pure coincidence.

Etiology. In regard to an eliciting cause for the original outbreak of association disease, irrespective of its mode of onset, we find only a few cases in which this was attributed to traumatism, fright, an infection or hardship. While this may mean pure sequence without the relationship of cause and effect it seems reasonable to suppose from analogy that such factors may have been contributory causes. The number of male subjects exceeds notably that of females but not to the extent that would warrant us in classing association disease under diseases of males. Since this male preponderance is not seen in the incidence of simple epilepsy we naturally associate it with possible absence of hysteria in families with association disease, which roughly suggests a mild immunity for females in these strains.

The age of onset is usually early in all familial disease in comparison with sporadic incidence. This we find to hold good in the association disease, for while simple myoclonus tends to appear at the age period, fifteen to thirty years, the myoclonus of the association disease supervenes much earlier. In cases in which the familial factor is most in evidence, the age of onset may be especially early

—from three years of age even, with an age period of three to eleven years.

Pathogenesis. The pathogeny of the disease has to do with the primary seat, the nature of the alteration and its cause. The subject is a most difficult one, for in addition to what is found in pure epilepsy there should be something to account for the myoclonic element. It is possible to incriminate the spinal ganglia, the basal ganglia, the cortex and even the cerebellum and medulla. Many authors have accused the cerebral cortex, while the spine seems excluded because of the absence of trophic muscle alterations, and also because the cloni cease during sleep. There are numerous anatomic or physiologic reasons for selecting the cortex as the seat of the process, but these need not be detailed here because there are equally valid reasons for accusing the basal ganglia, especially since the recognition of a myoclonic form of encephalitis epidemica; while the medulla and cerebellum have their advocates at the present time. There is no doubt whatever that lesions of the cortex can set up cloni which are of the same nature as those of myoclonus. Of the basal ganglia the striate body is the one which in theory should be associated with automatic and associated movements; or more justly this function is seated in the globus pallidus in which there are large motor cells. If the putamen and caudate nucleus of the striatum are the seat of lesions their function of inhibiting and coördinating these cells could be forfeited, with the production of automatic movements. This is what actually occurs in chorea while lesions involving the motor cells of the pallidus give rise to a Parkinsonian syndrome, both of these mechanisms being familiar to us in epidemic encephalitis.

Another neostriate symptom complex when both its cell types are involved in a destructive process is the Vogt syndrome, with its spastic diplegia, athetosis, rhythmic oscillations and paralysis of the pseudobulbar type. Finally, when the entire striate body is involved in a degenerative process, the Wilson syndrome is seen—progressive lenticular degeneration with tremor, rigidity of the Parkinson type with tonic and clonic spasms and occasionally choreic and athetoid movements—the tetanoid chorea of Gowers.

Pathology. Apparently the most recent summary of the findings in myoclonus epilepsy are those of Schultze in 1922. The lesions were scanty, vague and complicated. Changes in the cortex were evidently those found in ordinary epileptic dementia, which had been in evidence clinically. Changes in the basal ganglia are mentioned but were not decisive and there were also alterations in the cerebellum. All of these changes were degenerative in type and not peculiar to any one disease—simply more or less disappearance and degenerative changes in the cells with increase of the neuroglia. Volland, on the other hand, as a result of study of four autopsies found the cortex only slightly altered while there were also altera-

tions in the medulla and cord. The nerve cells in the anterior horns of the latter and those of the nuclei of the cranial cells in the medulla showed a migration of the nucleolus outside of the nucleus—even at times outside of the cell itself. He felt obliged to go back to the views of Unverricht as to the seat of the disease in the cord. Again Westphal and Sioli in an autopsy on a child found only some cell inclusions—corpora amylacea—within the ganglion cells and glycogen-like grains outside the latter. These were present almost universally but were most marked in the thalamus in the red and caudate nuclei. This was an unusual find, as the thalamus is seldom associated with any kind of motor anomaly.

It has not therefore appeared that the complication of myoclonus adds anything to the autopsy findings of degenerative epilepsy. When it was learned that epidemic encephalitis may be complicated by mild or severe myoclonus, it was thought that the latter might be brought into some definite relationship with lesions of the midbrain. This does not seem to have been the case. Clinically there are many forms of motor disturbance known to occur in encephalitis: myoclonus, chorea, choreo-athetotic movements, ordinary and Parkinsonian tremors but in most cases the disease runs its course without any of these complications. In regard to the autopsy findings of encephalitis, alterations may be present anywhere between the cortex cerebri and muscles inclusive. They are most marked and constant in the gray matter of the basal ganglia, midbrain and pons and especially in the region of the crura cerebri, extending toward the subthalamic and thalamic regions and down to the pons and bulb. However, contrary to what one would expect, the striate body is but rarely involved.

Symptoms. We next take up the symptoms of the association disease with the possibility of throwing light on its cause and nature. It is evidently immaterial which of the diseases is the first to appear for in one-half approximately epilepsy takes precedence, in one-third the two appear synchronously and in one-sixth myoclonus is first to appear, all of which seems to confirm the view that the two processes are virtually one with two expressions.

In comparing the epileptic and myoclonic components with pure epilepsy and pure myoclonus respectively, we find that despite the severity with which epilepsy could be present on so degenerate a substratum the disease may be incomplete in some cases while in others we see spontaneous improvement and even recovery, doubtless in a proportion higher than in pure epilepsy. Striking is the absence of an aura, which is present only when myoclonic movements behave as a motor aura. In the majority of cases the type of epilepsy at the onset is nocturnal although it may pass into the diurnal type. While this myoclonic motor aura is of common occurrence, grand mal attacks occur frequently without it. The seizures themselves are often incomplete and abortive or consist of

petit mal only although psychic equivalents are rare and retention of consciousness in paroxysms is common. Despite this absence of a psychic component, epileptic deterioration is very common, which fact alone would tend to show that the epilepsy of the association disease is true epilepsy. In this case it is impossible to see any necessary connection between the deterioration and the severity and frequency of the paroxysms.

The myoclonus component of the association disease, although this often attains its severest forms, is not necessarily of this type, for like the epilepsy it may be atypical—mild, incomplete and at times without the electrical character of typical myocloni. In other words the contractions vary from mild isolated twitchings involving portions only of muscle bellies to spasms of entire muscles, groups and numbers of groups, with locomotive effects sufficient at times to interfere with function and overturn the patient.

Good and bad days, which are common in most neurogenic affections, are evident here as well, but to a less extent than in simple myoclonus. In the association disease, owing to its progressive character, the good days tend to become fewer and fewer save in those patients who can obtain relief through various sedatives. In a few cases there have been actual remissions, so that patients were able to resume their occupation. On the other hand, at least as far as bromides are concerned, leaving off the remedy has led to a great augmentation of bad days, so that the patient has become completely incapacitated.

The will acts as a two-edged sword in these cases for while the patient may successfully inhibit some of the cloni and also call upon compensating muscles to steady the affected members, intention cloni may develop and aggravate the picture. When the disease has fully developed all voluntary movements are suppressed. The cloni never result in muscular hypertrophy as in athetosis and the opposite tendency to atrophy is often seen. A very rare form of the disease is characterized by muscular hypertonus and general tonic contractions replacing cloni.

Prognosis. Under the head of prognosis may be mentioned the following tendencies: Malnutrition, precocious senility, dementia, general abridgment of life, pulmonary congestion, sterility and polymortality of children born. Nevertheless there may be long years of remission in some cases. Death from ordinary intercurrent diseases is often seen both in the patients and in their progeny. The bad prognosis appears to show a restricted capacity for survival irrespective of the effects of the disease on the vitality of the individual.

Diagnosis. The diagnosis should throw some light on the nature of the association disease by bringing the latter in rapport with similar affections. Save in the confirmed case there should be a period of observation before the physician commits himself to a

diagnosis. It is an error to depend on familial incidence, for sporadic cases are common although in the latter there may be no opportunity to arrive at a definite knowledge of the patient's kin or there may be too few kin to reach a conclusion as to the possibility of a familial character.

In the first place typical epilepsy may be associated with symptomatic myocloni without any reason to believe that the association disease is present. These patients may exhibit only abortive cloni or pseudomyoclonus, limited to jerking movements of mere twitches of muscle bellies or the motor manifestations may be classed as chorea or tics. Some of the older epileptologists in describing these muscular movements under such names as tremors, idiomuscular contractions, etc., may have included cases of true association disease and until we know more of the nature of the latter it is proper to regard the two modes of behavior as having a common origin and nature. The false cloni are chiefly limited to the muscles of the upper extremity and to the flexors and show symmetry, while they lack the electrical character of true cloni. It is not necessary to regard all of these cases of muscular jerks and twitchings as a rudimentary myoclonus for on a deeply degenerate stock there is no reason why an epileptic should not coincidentally suffer with tics and degenerative types of chorea; but in cases where our diagnosis is in abeyance, and this experience is common, it is impossible at times to escape the conviction that we are in the presence of an atypical association disease. We will return to the subject of motor manifestations but will first allude in passing to the confusion of the association disease with hysteria. Typical myoclonus has been seen in subjects notably hysterical and should such patients also suffer from hysterical convulsions a mistake in diagnosis might readily occur. We have already spoken of the rarity of hysterical cases in the families of patients with the association disease and as far as we know there has never been a case of the latter in practice which was confused with hysteria. Unverricht isolated a child of an association disease family from its brothers and sisters, thinking it possible that psychic contagion is a factor under such circumstances, but she developed the disease in spite of this separation. Should one of our patients with the undoubted diagnosis of myoclonus epilepsy be found later to have hysterical stigmata the fact would for the time invalidate the diagnosis.

To return to the association of true epilepsy with false cloni, the author in an experience of several thousand cases of the former has never seen an epileptic with true chorea and hence is inclined to believe that the alleged cases of choreic epilepsy are myoclonic. It is true, however, that epilepsy has now and then been seen in Huntington's chorea which will be mentioned later. When epileptics exhibit tics these are limited to the facial muscles and are stereotyped in character, seldom showing any variation.

The victim of progressive paresis may at various times show both epileptiform convulsions and myocloni and thus might conceivably be regarded as having association disease but in practice such a blunder is not likely to occur.

Since the Huntington's chorea of textbooks appears relatively late in life and without any suggestion of an epileptic component it is not likely ever to be mistaken for myoclonus epilepsy, although it is eminently familial and attended with mental deterioration. Its relationship to myoclonus epilepsy is not one of differential diagnosis so much as of a common soil. However in recent years and with advancing knowledge of degenerative chorea it has been noted that some cases of the latter begin early in life, that the choreic movements may sometimes show a myoclonic quality and finally that epilepsy, however infrequent, may be a complication. Foerster, Lundborg and others have discussed exhaustively the relationship between the two affections and while the former is a unicist, actually believing in the identity of the two, Lundborg insists that they are wholly distinct. Hoffmann, Schultze, Remak and Jolly have seen cases in which the differential diagnosis was by no means easy. In regard to common autopsy finds Schultze found that these were very similar, for in both types there are lesions of the basal ganglia and in both the changes in the cortex accord well with the mental deterioration common to both processes. At present it may be claimed that the two are cognate, occurring in the same stock although at different age periods and with different muscular movements and a different association with epilepsy, yet shading into each other in such a manner that a radical differentiation is hardly possible.

Treatment. Anything like radical treatment either with medical or surgical resources is out of the question and as a matter of fact any kind of surgical intervention, especially trephining, is contraindicated because of uniformly bad consequences, as stated by Rabot. The use of drugs sometimes causes prolonged remissions from one or both components and bromids if properly given will be of value in the great majority of cases. This means that 1 to 2 drams of the drug must be given daily over long periods of time. This control of the myocloni may or may not mean that the association disease is a unit affection and not a complication of two different diseases. The greater degree of improvement is seen in the epileptic component. The myocloni become less severe and persistent save in a few cases in which even when the dose is pushed there is no response. The use of the salt-free diet will lower the requirement of bromid and this may also be given in the form of a bromipin, a nutritive emulsion which contains 10 per cent of bromid in oil of sesame. The addition of chloral or opium to bromid is of value in some cases. The former is added to the bromid in small doses in the evening especially in cases in which the cloni are worse

at night. Opium is of use only in the Flechsig opium-bromid treatment. These drugs are of use purely as synergists and have not shown much value when given alone. Alcoholic excesses aggravate and even seem to evoke myoclonic spasms, but paradoxically a drink will sometimes brace up the patient for the time being although this use of alcohol cannot enter into the treatment as such. If a patient take several drinks he will very likely suffer from an exacerbation of cloni while the effects are wearing off. Coffee appears to exert a more striking effect in this respect and may often abort threatened contractions; taken early in the morning this remedy may even change a "bad" to a "good" day. It should be drunk before the patient rises and with some light repast. The use of coffee in excessive amounts does not appear to aggravate the cloni. Of late years luminal has been used widely, both in small and large dosage, with excellent effects. The small dose which suffices to control epilepsy does not always show a corresponding effect over the myocloni but if large amounts are given for a short time the latter may sometimes be suppressed altogether, repeating the treatment after a short interval. These patients may tolerate a dosage of luminal at least five times that usually required for epilepsy alone.

Various resources of physiotherapy are of value in special cases, such as electricity, baths, massage and passive motion, and rest. Diet in the main should be simple and bland, a milk regimen being indicated as a rule, but forced feeding and underfeeding may have a place. The salt-free diet has already been mentioned as useful to keep down the dose of bromids. If the muscles involved in eating and swallowing are unable to function, rectal or nasal feeding may be required. When a patient is in the midst of a good spell it may be well to overnourish him, keep him abed and give him massage to discount the ill effects of the bad days which will follow; while a patient already bedridden will profit by massage and passive motion. Those still able to be about can keep down their myocloni by avoidance of cold and exposure, fatigue and the painful emotions.

Case Reports. We may now proceed to give in abstract four personal cases of the association disease.

CASE I.—A[1] woman, aged fifty-two years. The disorder was familial in type and three other children in the family stock (first cousins) developed the association disease which was described by them as "St Vitus' dance and fits." On the maternal side there were several cases of insanity in near relatives. The parents of the patient were first cousins. There was no direct inheritance of any serious character and the history mentions no siblings. The patient had been a strong child and made the grades in school without difficulty. At the age of thirteen years she presented her first grand mal epileptic seizure, a nocturnal one, and the myoclonus must have set in at nearly the same time and may have antedated the epileptic attack. It began in the arms and after its inception was more or less constant, although showing much variability, with good and bad days. She had

[1] This case was originally reported in the Review of Neurol. and Psych., 1907, **5**, 532.

first seen her myoclonic cousins several months before her own outbreak and was much perturbed by it, but there is no reason to assume the existence of an affective element. Such meetings among relatives are natural and in similar cases in which isolation has been practised the subjects have duly developed the familial disease. To characterize the fluctuation of the myoclonus from day to day, it may suffice to state that on bad days the arm movements interfered with piano practice. The myoclonic jerks were gradually generalized throughout the muscles but the order of implication was not recalled. In regard to the epileptic component, this was severe at the outset but after the first year it became milder so that from fifteen to forty-two years of age the average frequency of the seizures was one a month including petit mal attacks. After this period and up to fifty years, her age when the case was first seen, the epileptic attacks became reduced in frequency to eight annually, including grand and petit mal, and nocturnal and diurnal seizures. At the outset of the disease the myoclonic movements became aggravated progressively some days before the epileptic seizures, while for a few days after the latter she was quite free from myoclonus. After the first two or three years, however, the two diseases seem to have pursued their courses independently. The epilepsy led to no mental enfeeblement. Myoclonic movements were in evidence in some form and degree daily, but the affection did not seem to have progressed far. The bad days, however, seem to have grown worse so that for certain short periods there was a veritable status myoclonicus during which she had to remain in bed. There was never any myoclonus during slumber. The movements seem to have been favorably influenced by bromids and chloral which she took for the first thirteen years, and also by coffee. However, she gave up the use of all medicines and became a Christian Scientist without either aggravation or apparent improvement. She was free from other nervous manifestations and hysteria, although she suffered from nocturnal enuresis until the age of thirty-one years, this symptom ceasing spontaneously. Mental stress and emotion seemed to aggravate the myoclonus, and also hot and cold weather. The mildest cloni were fibrillary twitchings of single muscles. At the other extreme all of the muscles participated almost synchronously in a manner which defied description, those of the trunk and proximal aspects of the extremities being most involved. There was slight asymmetry of the two sides so that the body and head may be hurled, for example, to the right. In the height of a paroxysm the facial muscles may participate. After the series of bad days known as the status myoclonicus, the muscles were sore and the patient became exhausted. At times there was much interference with function; swallowing was prevented, and food or drink forcibly ejected. Through the participation of the respiratory muscles there was an interference of the speech. The patient was at times thrown to the ground and sustained severe injuries. The acme of the myoclonic contractions appeared to take place in the rectus muscles of the trunk, the spasms at times being painful. The handwriting was characteristic of myoclonus with the so-called rockets and somersaults. The patient endeavored to control these hand movements by holding the right hand with the left, but the handwriting was still characteristic of the disease.

Case II.—A female, aged seventeen years, is a feebleminded, chronic and atypical myoclonus epileptic, who has had two periods of status myoclonus. Her maternal grandmother died insane at forty-three years; her mother became insane and was always subject to migraine. Her father "had epilepsy for a year," its onset appearing at twenty-three years, he had always been nervous and rheumatic, and committed suicide. A sister and brother died of unknown brain disease in infancy. The patient was the youngest, born full term, normal labor, although it is reported that she weighed

17 pounds at birth. Dentition was difficult but no convulsions occurred. She walked at three years of age. At six the first epileptic seizure was noted and was supposed to have been induced by fright; thirteen days later there was a second seizure. Thereafter attacks, typical of grand mal, occurred about every two weeks. The patient had myoclonic spasms "ever since she could remember, before the epilepsy began." A slight bilateral ptosis has existed since the myoclonus. She was under my observation for three and a half years. The seizures were always preceded by myoclonic contractions, and were classic grand mal. The muscles usually involved in the clonic contractions were the biceps, triceps, deltoid, and pronators of the forearm; the quadriceps and adductors of the thigh; the pectorals and occasionally the recti abdominales, the sterno-cleido-mastoid and digastric of the neck and the zygomatics and buccinators of the face. There was often a bewildering muscle play over the entire body. The muscle spasm was short, sharp, lightning-like, arhythmical, asynchronous on the two sides, and implicated most intensely the proximal muscles of all the extremities. As the patient endeavored to control the muscular spasm in standing, the foot was suddenly raised, drawn back, or stamped more or less violently as though she were preparing for a drill in marching, and a diaphragmatic grunt was occasionally heard. The myoclonic spasm was continuous in the waking state; and was slightly controlled by the will for a few seconds, but was then intensified. The contractions had nodes of clonic intensity up and down these inclined planes, the muscular movements constantly traveling in more or less shorter periods of time (20 to 30 a minute); loss of consciousness occurred and the patient had an epileptic attack of varying severity. On two occasions, separated by an interval of two years, she had a rapidly recurrent series of myoclonic spasms constituting a status myoclonus. The contrast of this status with that of her status epilepticus is striking; the cardinal symptom curves were not dissimilar, but the ratio between the curves and the myoclonic contractions were not the same as that of an equal number of epileptic seizures. As the climax of each paroxysm approached, the whole body was hurled by the spasm to the right. There was no rigidity and no convulsions appeared in the forearms or legs, but the shoulder, arm and thigh muscles were in violent agitation, the arms and legs being tossed about in the most distressing manner. At times a clonic movement in the masseters caused the teeth to chatter. The patient was perfectly conscious throughout the status, and often complained of severe muscular pain and nausea at the acme of the crises. The dilated pupils always responded to light. The diaphragmatic spasms often caused projectile vomiting at the crises of several paroxysms forming the status. During certain crises of myoclonus the contractions of the abdominal muscles were so sudden and intense as to cause urine to be voided, to the evident distress of the patient. Each paroxysm lasted fifteen to twenty seconds and consisted of from 40 to 50 most intense clonic movements. The face was flushed throughout, and the body was covered with a profuse perspiration. The patient lost several pounds in weight and remained physically and mentally exhausted for twenty-four hours before regaining her usual prestatus condition. The contractions were almost entirely absent for four days following the status periods.

Case III.—A male imbecile, aged nineteen years, colored, developed epilepsy and myoclonus simultaneously at seven years of age, after scarlet fever. The father and mother were both feeble minded but had no disorder of motility; a brother was idiotic. Multiple stigmata of degeneration existed. The patient came under my personal observation but seven days before death, and a knowledge of his early history could not be obtained. The epileptic attacks were reported by his physician to be classic, and

occurred every other day; they were of the petit mal and grand mal types. They were always preceded by an increase of the myoclonic contractions and were followed by a temporary cessation of spasms for one to three hours.

The patient was bedridden when first seen. The arms and legs were considerably emaciated; myoclonic contractions, involuntary and irrepressible, affected the trunk, neck and thigh muscles. The clonic contractions were shocklike as though electrically produced and were locomotive in effect. Usually the patient was entirely free from spasm at intervals when allowed to remain perfectly quiet, while asleep and while under the effect of bromids. Voluntary movements and attempts to walk induced a veritable paroxysm of clonic movements; oftentimes only certain muscles or parts of muscles participated. Contractions were irregular and not synchronous, but were always bilateral. The lower face about the mouth especially, was involved in the more general and intense paroxysms. Attempts at speech caused such a series of spasms that the patient ejaculated only about half a dozen words while under observation; usually such attempts ended in an unintelligible jumble of words. He could not stand alone, but the contractions ceased for a time when he was held upon his feet. Efforts to walk always caused violent contractions, the patient clutching wildly for support. No epileptic paroxysms occurred while he was under our observation, as bromids were given constantly in an effort to suppress the myoclonic contractions.

Examination of the chest showed an advanced stage of tuberculosis. The diaphragm was noticeably affected and the peculiar myoclonic grunt was typical. He could not feed himself nor could he move about in bed in the slightest degree without inducing a series of three or four severe clonic spasms. The reflexes were uniformly exaggerated. The remainder of the examination was negative. On the eighth day after coming under observation he died from tubercular pneumonia.

The infrequency of choreic epilepsy, the rarity of chorea in the negro, and the typical symptoms of both myoclonus and epilepsy which were controlled by bromids makes the diagnosis of myoclonus epilepsy certain.

Case IV.—A male, aged twenty-two years, developed myoclonus at seventeen, and epilepsy at twenty years. All his paternal relatives were healthy. The maternal grandfather developed myoclonus at twenty-five and died of the disease at forty-six years; the myoclonus was described as being of such a nature that he often injured himself and others with tools when so employed. He grew steadily weaker in body and mind and was bedridden a year before his death, which took place from exhaustion; there was no epilepsy in the grandfather's case. An uncle and our patient's mother were the only children of the grandfather's family. The uncle was healthy and had a family of five robust children. The patient's mother, although not very strong, never had any illness until the birth of our patient, her second child. The elder brother was healthy until his death from appendicitis at eighteen years. The mother developed myoclonus soon after the birth of our patient at the age of nineteen years, and within a year thereafter had classic epileptic attacks once or twice weekly. Bilateral ptosis developed with the advancing development of the myoclonus, a symptom also shown in our patient. The disease in the mother progressed rapidly and ran its course in three years; she was bedridden for two years before death, which also resulted from exhaustion induced by the myoclonus epilepsy. Our patient was a normal full term child, born after a difficult labor of twelve hours, although no instruments were used. He had convulsions during dentition at two years, but otherwise was healthy until seventeen years of age, when great physical and mental lassitude developed in marked

contrast to the patient's former athletic disposition, since before he had excelled in swimming, baseball and football contests. After these athletic exercises, at sixteen years, his arms "often trembled and the shoulder muscles quivered." After discontinuance of athletics the tremblings became worse than before, even when no exertion was made. In a few months the myoclonic manifestations began, especially in the upper extremity, being most marked in the right arm. The contractions at first were clonic, arhythmical and paroxysmal with free periods between the paroxysms, but as they extended over the body in the next few months their decidedly paroxysmal character ceased. The patient was then rarely free from contractions in some part of the body during the waking state, although there were days of varying intensity of spasms. In six months from the onset the whole body became affected; the voice trembled also; the face and neck were last and least affected from below upward. At twenty-one years the diaphragm was involved in the myoclonus, causing the patient to emit the sound "ahem." About this time he also developed difficulty in swallowing, he emaciated rapidly and became bedridden. He was fearful of making an attempt to walk or even stand. He ceased to make any effort to write at the onset of the myoclonus. Soon after this he developed classic grand mal epileptic paroxysms, which were always preceded by a gradually increasing intensity of the myoclonic contractions. Despite a progressive mental enfeeblement, commensurate with his disease, his intelligence was always above that of his appearance.

An epileptic paroxysm, occurring while under observation, presented the following points: The attack occurred just after dinner. The myoclonic contractions of the pectoralis major, biceps, the quadriceps extensor and the muscles of the face were all much exaggerated for one hour before the attack. The contractions gradually increased in intensity, until the seizure began with a short period of tonicity, lasting from twenty to thirty seconds. The epileptic convulsion was most marked in those parts previously engaged most intensely in myoclonic contractions. The tonic stage was followed by clonic convulsions for a period of two minutes, which in turn was replaced by deep stertor and coma. The patient slept for one hour after the convulsion had ceased and then awoke quiet; his mind was clear and the whole body was entirely free from myoclonic contractions. In five hours, however, the myoclonic contractions began again. Both the myoclonus and the epileptic attacks were benefited for a time by bromid, but chloral had no effect on either. After forced swallowing the patient gained several pounds in weight, but as swallowing became more difficult diarrhea and emaciation again set in; for several days he was in a condition of almost continuous clonic spasm, a form of status myoclonus. As the temperature began to rise the myoclonic contractions ceased and the comatose state of the status myoclonus began, and he finally died of exhaustion and pulmonary edema, induced by the status myoclonus.

Conclusions. 1. The association disease—myoclonus epilepsy—constitutes a syndrome of a cortical and midbrain disorder, and either the myoclonus or the epilepsy may begin the clinical picture, but when the disease is well established both syndromes are disproportionately present.

2. Its etiopathology is cleared up only in part, and what knowledge we have is largely due to the opportunities to study the presence of myoclonic features in the autopsy material of encephalitics. The epileptic aspects are still left in the postulate of a cortical lesion either related to or independent of the affected midbrain centers.

3. The epileptic part of the syndrome would seem to be recruited from a very intensive degenerative family stock, wherein the immediate excitants of the convulsive attacks are even more to be discounted than in idiopathic epilepsy. The combination of pathologic symptoms in these two essentially correlated centers is still a question of either the preponderance of the myoclonus or the epilepsy, of which either is considered as an appanage. The best hypothesis to account for the disorder is that the total brain function is injured and that the expression of the disease in this complete syndrome is but a *symptomatic pathology* of a still more indefinite chemical or degenerative epilepsy.

4. Aside from psychogenic reëducational plans of treatment, the best temporary and comforting treatment for the disorder is the employment of sedatives and especially the judicious administration of the combination of chloral and bromid. The condition is probably the best example that exists today of combined syndromes of motor and sensory types of defect of brain function.

LESIONS IN RABBITS FOLLOWING THE INTRAVENOUS INJECTION OF BACTERIA FROM CHRONIC PERIAPICAL DENTAL INFECTION.

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The theory of focal infection postulates the presence in the body of a localized area of infection harboring bacteria capable of producing systemic disease. Organisms in chronic foci vary widely in pathogenicity. Some idea may be gained concerning the virulence of the infecting organism by a study of the extent and severity of the lesions in the host. Clinical symptoms and signs are, however, the result of an interaction of the resistance of the host and the virulence of the infecting organism. The clinical manifestations show only indirectly the disease-producing power of the bacteria. The best comparative data on the pathogenicity of the organisms from chronic foci are gained from the results of the inoculation of animals. With this idea in view, I have studied the lesions in 1500 rabbits injected intravenously with organisms from chronic dental infection.

Several investigators have studied the lesions in animals following the intravenous injection of bacteria recovered from chronic foci and from systemic lesions resulting from focal infection. The series usually have been small and studied primarily for the involvement

of some one organ. Henrici[1] has well summarized the literature on the subject, and added the results of the injection of 225 rabbits with streptococci from various sources. Rosenow[2] reported on the injection of 156 rabbits with 42 strains of streptococci from dental infection. Meisser and Gardner[3] studied the lesions in 256 rabbits injected with 100 strains of streptococci from infected teeth. The latter workers have studied especially the tendency to elective localization. Other workers have been less successful in producing lesions in animals with organisms from chronic foci.

In determining the virulence of organisms for the host by animal inoculation it is vitally important that the cultural conditions under which the organisms are grown in the interval between removal from the host and injection into the experimental animal be most favorable. This necessitates a short interval of time for the culture, the use of medium with proper nutritive qualities and a gradient oxygen tension. These requirements have been emphasized repeatedly by Rosenow. By far the most desirable mediums for this work are glucose brain broth and glucose brain broth agar. These are almost specific for the streptococci found in chronic foci.

Bacteriology. In making the bacteriologic studies of tooth infections I have followed closely the methods of Rosenow. All cultures have been made in glucose brain broth, prepared according to Rosenow's directions:

Glucose Brain Broth. Dehydrated bactonutrient broth, 8 gm.; sodium chlorid, 8 gm.; dextrose, chemically pure, 2 gm.; Andrade indicator, 10 cc.; distilled water, 1000 cc. The broth and salt are dissolved by heating. After cooling, the indicator and dextrose are added. The medium is tubed in 6 by ¾-inch test tubes, so that the depth is at least 3½ or 4 inches. Three pieces of calf brain, about 1 c.mm. square, and two or three pieces of crushed marble are added to each tube. The tubes are then sterilized for twenty minutes in the autoclave at 20 pounds' (9.07 kg) pressure.

Glucose Brain Agar. The agar medium is made by adding 7 gm. of powdered agar to 1 liter of glucose brain broth, prepared as indicated above. The calf brain and marble are then added and the medium is sterilized.

The brain substance renders the bottom of the medium anaërobic; the top is aërobic, so that every degree of oxygen tension between these two points is provided. The nutritive qualities of these mediums are especially favorable for the growth of the organisms encountered in infections about the teeth.

In making cultures of tooth infections the greatest care is necessary to avoid surface contamination. We have found that sterile cultures can be quite uniformly obtained from the root tips of anterior vital teeth by the procedure which we have employed. It is apparent that unless sterile cultures can be obtained from non-infected vital teeth, cultures of pulpless teeth are of little value.

We have utilized the following technique. Before extraction the teeth are thoroughly scrubbed with gauze, after which the field of operation is painted with tincture of iodin. Care is taken that the iodin penetrates well into the space between the gum margin and tooth, and between the teeth. The iodin is removed with alcohol and the area of operation walled off with sterile gauze.

The top of the extracted tooth is cut off with sterile forceps directly into a test tube containing a few cubic centimeters of sterile salt solution and a small amount of sharp sand. The tubes are well shaken to macerate the tissue on the end of the tooth as completely as possible. The mediums are inoculated by pouring the salt solution containing the suspended tissue into a tube of glucose brain broth. The inoculated tubes are incubated at 37° C. for twenty-four to forty-eight hours. A smear is made from the broth culture and stained by Gram's stain (Fig. 1).

Rabbits have been injected intravenously with the broth culture as soon as a good growth was obtained. This was never more, and usually less than twenty-four hours. When cultures were taken from several teeth from 1 patient the several broth cultures were often mixed before injection. The rabbits varied somewhat in size, but averaged about 1500 gm. Each animal was given 5 cc. of the broth suspension.

The animals have been watched carefully for lesions. Usually necropsy was performed on 1 animal from each culture three days after the injection and on the second six days after injection. Occasionally animals have been kept for longer periods for observation. At necropsy the animals were carefully examined for lesions. No lesions were considered as present unless plainly visible to the naked eye. Microscopic sections have been made of many of the tissues. Cultures have often been made of the organs at necropsy but not routinely.

It is apparent that the virulence of the organisms will vary somewhat with the class of patients from which the material is drawn. Thus, one would expect more virulent organisms in the foci of patients presenting clinical evidence of systemic disease resulting from focal infection. Our material was obtained from patients entering a pay dental clinic. These were largely ambulant patients who came primarily for dental treatment. Others while ambulant were referred by physicians for the removal of foci which were considered related etiologically to systemic disease. Some were hospitalized patients.

Experimental Observations. Fifteen hundred rabbits have been injected with the cultures from 501 patients. At least 2 rabbits were injected from each patient. Of the total number injected, 289 died, usually within twenty-four hours after the injection was made; others died in from forty-eight to ninety-six hours; 285 showed at autopsy no lesions of any kind. Many of these were

animals dying soon after injection. The incidence of lesions in the entire group is shown in Table I. It is of interest to note that the

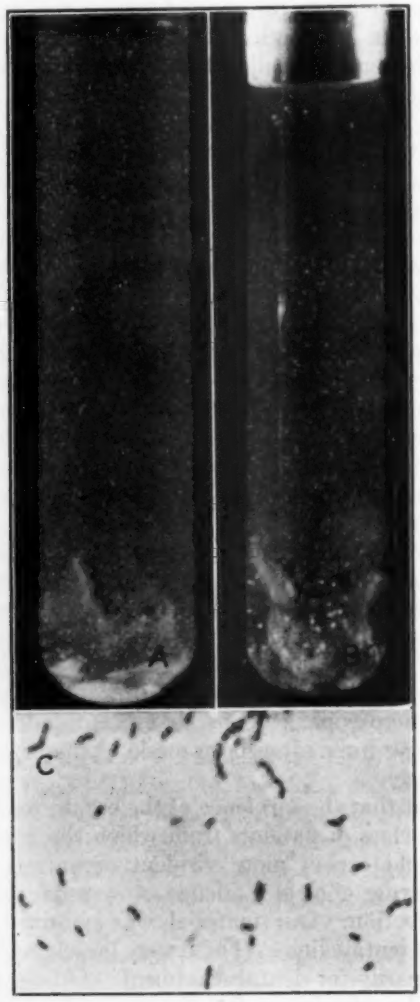

FIG. 1.—*A*, Culture from periapical dental infection in deep tube of glucose brain agar. Note the uniform growth throughout tube; *B*, culture similarly made from another tooth. This organism will not grow in the aërobic zone, as shown by the absence of colonies at the top of the agar column; *C*, typical short-chain streptococcus from a periapical infection.

frequency of lesions in the rabbit parallels closely the incidence of lesions as observed clinically in man. The lesions observed are discussed more fully below.

TABLE I.—LOCALIZATION OF BACTERIA ISOLATED FROM DENTAL INFECTION.

No. of animals.	No. of patients.	Percentage of animals showing lesions.							
		Joint.	Kidney.	Muscle.	Endocardium.	Myocardium.	Brain.	Eye.	Stomach and duodenum.
1500	501	58	30	21	18	10	4	14	16

Joint. Eight hundred and sixty-five, or 58 per cent, of the total number of animals injected had joint involvement. This consisted of a distention of the joint capsule with purulent fluid (Fig. 2, *A*, *B*) or multiple hemorrhages in the synovial membrane and joint capsule. Stained films of the cloudy fluid showed many pus cells and often bacteria. Two hundred and thirty-five showed joint lesions only; the remainder also had other organs involved.

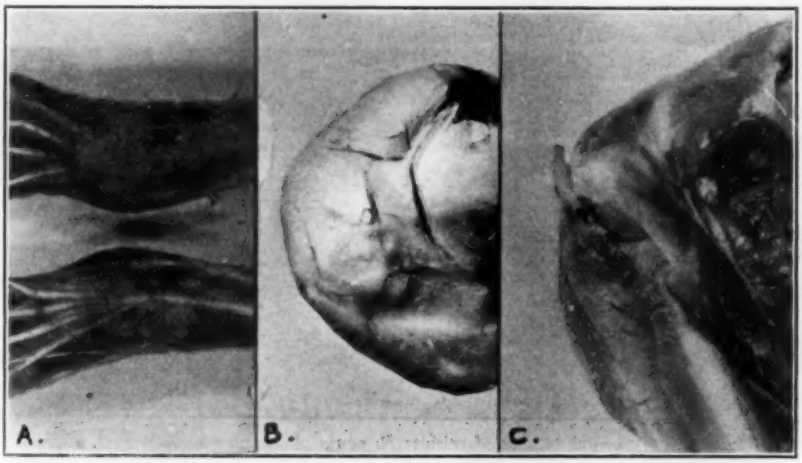

FIG. 2.—*A*, acute arthritis of wrist joint of rabbit; *B*, acute arthritis of knee joint with areas of necrosis in muscle fibers; *C*, chronic proliferative changes in knee joint several weeks after intravenous inoculation.

A record was kept of the location of the joint lesions in 200 animals; 123 of these showed gross evidence of joint disease; 41 had involvement of the knees, shoulders and elbows; 13, of the knees only; 28, of the shoulders only; 11, of the shoulders and elbows; 29, of the shoulders and knees; 1, of the elbows only. Animals allowed to live sufficient time often showed chronic changes in the joints (Fig. 2, *C*).

Kidney. The kidney also showed a high incidence of lesions. Four hundred and fifty-three (30 per cent) of the animals injected showed at autopsy gross kidney lesions. By far the most common type of lesion has been pyelonephritis, manifested as edema, necrosis and abscess formation in the medulla of the kidney (Fig. 3, *F*, *G*, *H*), and usually extending down well to the tip of the papilla. Multiple cortical abscesses (Fig. 3, *C*, *D*) were also frequently

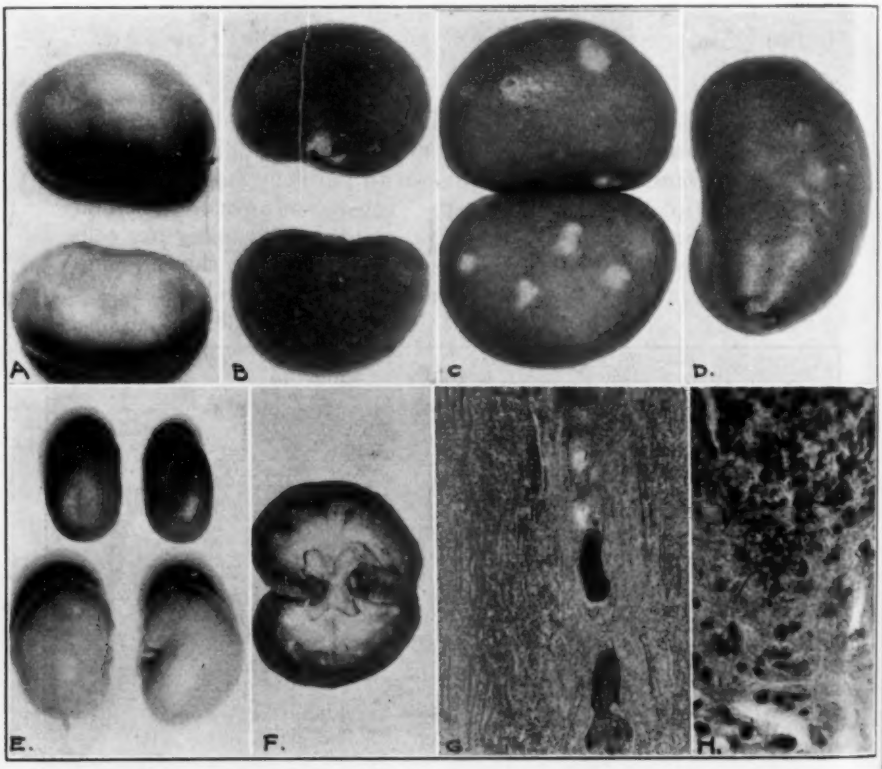

FIG. 3.—*A*, normal kidney of rabbit; *B*, acute glomerular nephritis; *C*, cortical abscesses; *D*, abscesses and hemorrhages in cortex; *E*, subacute parenchymatous nephritis (below) compared with normal kidney; *F*, abscesses in medulla of kidney; *G*, photomicrograph of lesion in medulla; *H*, organisms in lesion in kidney. (Gram-Weigert stain.)

seen. Other lesions observed were: acute hemorrhagic nephritis (Fig. 3, *B*), sub-acute parenchymatous nephritis (Fig. 3, *E*), hemorrhages in the medulla and perinephric abscess.

Muscle. Gross muscle involvement was observed in 315 (21 per cent) of the animals injected. The lesions appeared usually as small white streaks (Fig. 4, *A*), best seen in the freshly killed animal. These were found most commonly in the muscles of the

extremities. Not infrequently lesions were found also in muscles elsewhere. Sections of the involved areas showed necrosis of the muscle fibers without marked cellular infiltration. Gross hemorrhages in the muscles were seen occasionally (Fig. 4, *B*).

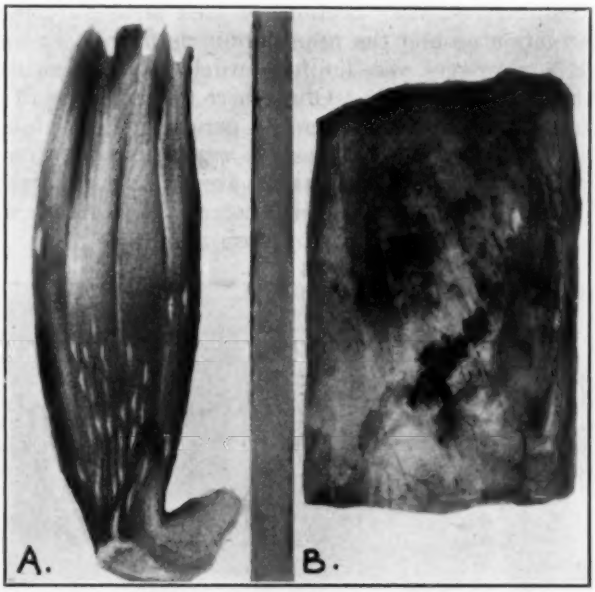

FIG. 4.—*A*, typical short steaks of necrosis in voluntary muscle; *B*, hemorrhages in muscle of shoulder.

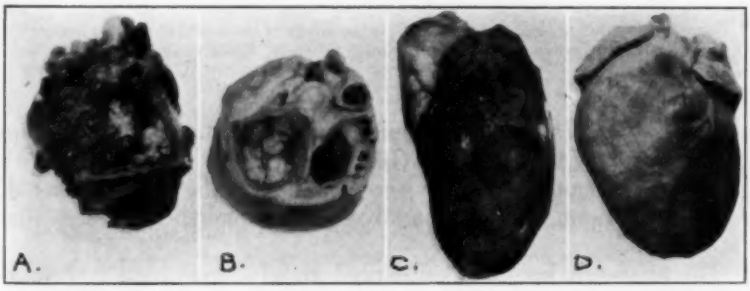

FIG. 5.—*A*, vegetations on leaflets of tricuspid valve; *B*, very large vegetations almost occluding the valve orifice; *C*, hemorrhages in the musculature of the right auricle only; *D*, massive necrosis of muscle fibers of right ventricle.

Heart. Three hundred and fifty-three of the 1500 animals showed at autopsy some heart lesion. In 60 both the heart muscle and the endocardium were involved; 258 showed lesion of the valves only; 155 had myocardial disease only. The valvular lesions were almost entirely vegetations, often of large size (Fig. 5, *A*). Occa-

sionally they were large enough to almost completely occlude the valve opening (Fig. 5, *B*). Occasionally only hemorrhages at the base of the valve were found.

The myocardial lesions consisted of discrete hemorrhages or of short white streaks of necrosis (Fig. 5, *D*), similar to those observed in the voluntary muscle. Sections of such areas showed marked cellular reaction around the necrotic muscle fibers. In some animals the hemorrhages were limited entirely to the musculature of the right auricle (Fig. 5, *C*). Often there was an excess of pericardial fluid. Occasionally a purulent pericarditis was found. Of 24 rabbits having valvular lesions the vegetations were on the tricuspid valve of 17 and on the mitral valve in 7. In 13 rabbits the type of myocardial involvement was noted. Hemorrhage only was observed in 6, and areas of focal necrosis only in 7.

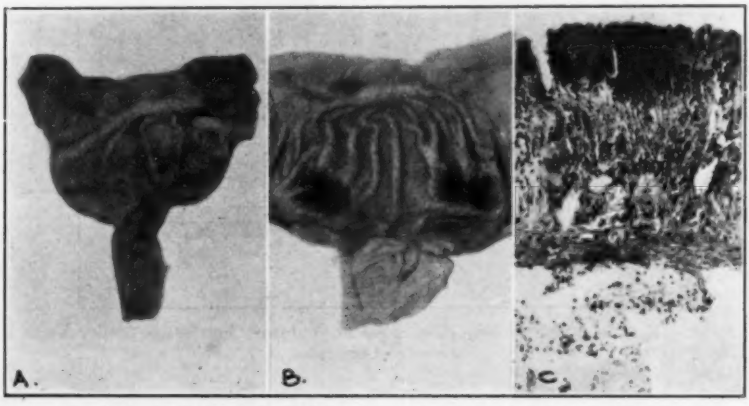

FIG. 6.—*A*, small ulcers of stomach; *B*, large ulcers of stomach; *C*, photomicrograph through stomach lesions showing superficial necrosis, hemorrhage and edema with cellular infiltration.

Stomach and Duodenum. Lesions of the stomach or duodenum or of both were found in 234 (16 per cent). Of 224 animals with such involvement, the lesions were confined to the stomach in 153, to the duodenum in 56 and involved both stomach and duodenum in 14.

The anatomic lesions, as observed grossly, were usually hemorrhages with or without ulceration. The lesions in the stomach nearly always showed ulceration or at least erosion (Fig. 6, *A*, *B*). The hemorrhage in the duodenum usually was not followed by gross ulcer formation (Fig. 7, *A*, *B*, *C*, *D*). The course of the pathologic process after the initial injury depends largely perhaps on the amount of free hydrochloric acid present. In some animals the lesions consisted principally of necrosis in the muscle wall, a type of lesion commonly found in the voluntary muscle.

Sections of the involved parts show hemorrhage, polymorphonuclear infiltration and necrosis of the mucosa (Figs. 6 and 7, *E*). The pathologic process is usually quite diffuse, and evidently not usually dependent on thrombosis or embolism. It is often assumed that damage here by bacteria must be due to one or other of these two conditions.

Eye. Two hundred and four (14 per cent) of the series showed gross eye lesions. The eye involvement is high because a large number of animals were injected with cultures from patients suffering from acute metastatic eye infection. The most common anatomic lesion was an iritis or iridocyclitis (Fig. 8, *B*, *C*, *E*). Some animals showed multiple hemorrhages in the iris, limbus (Fig. 8, *H*) or sclera, cloudy fluid in the anterior chamber (Fig. 8, *F*), cloudy cornea and hyalitis (Fig. 8, *D*). Pericorneal injection often

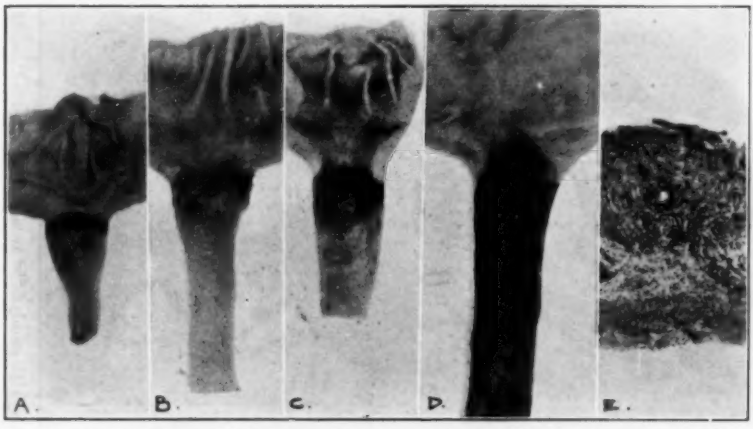

FIG. 7.—*A*, *B*, *C*, *D*, multiple hemorrhages in duodenal bulb; *E*, photomicrograph of lesion in duodenum.

developed a few hours after the inoculation. In some animals the injection was progressive; in others it disappeared only to reappear at a later date with evident signs of an active infection. Histologic examination of the eyes showed injection of the vessels or hemorrhage in the iris and ciliary body in some specimens. Others showed the diffuse inflammation of a panophthalmitis (Fig. 8, *G*), including at times the extraocular muscles. Still others showed marked cellular infiltration of the choroid humor. One showed only an infiltration of cells in the vitreous humor.

Nervous System. Sixty-two (4 per cent) of the total number injected showed gross brain lesions. The most common lesion was a basilar meningitis (Fig. 9, *C*, *D*) manifested clinically by restlessness, irritability and choreiform movements. At autopsy the cerebrospinal fluid was cloudy and an exudate present on the base of

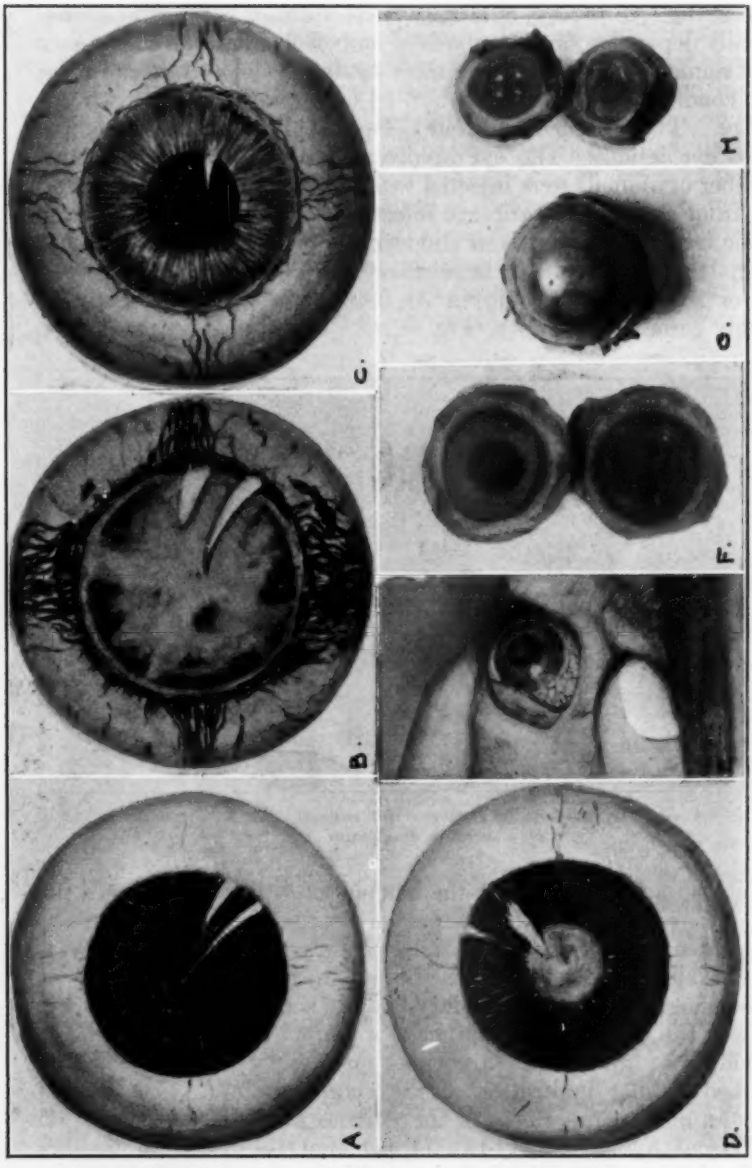

FIG. 8.—*A*, Normal eye; *B*, acute iritis with exudate in anterior chamber; *C*, subacute iritis; *D*, hyalitis; *E*, photograph of rabbit's eye showing acute iritis; *F*, eye of rabbit with exudate in anterior chamber (above) compared with normal (above); *G*, panophthalmitis; *H*, hemorrhages in limbus.

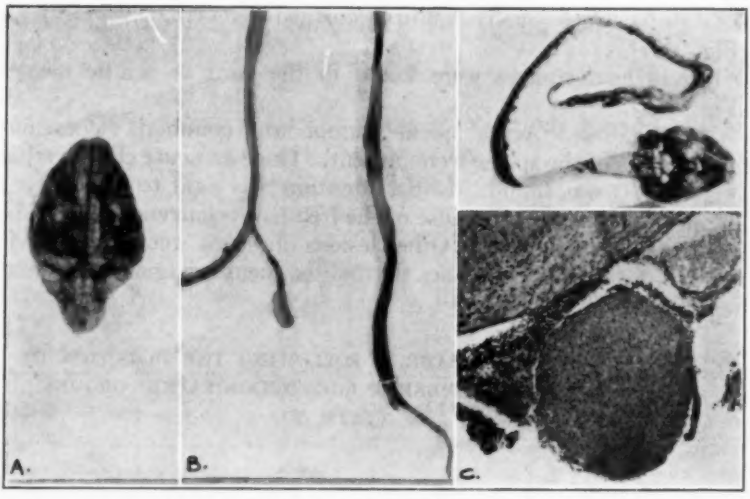

FIG. 9.—*A*, multiple hemorrhages in brain; *B*, hemorrhages in sciatic nerves; *C*, brain and spinal cord of rabbit (above) showing hemorrhage in caudal end of cord and in brain. Below, photomicrograph of section through base of brain shown above. Note the cellular infiltration around the cranial nerve.

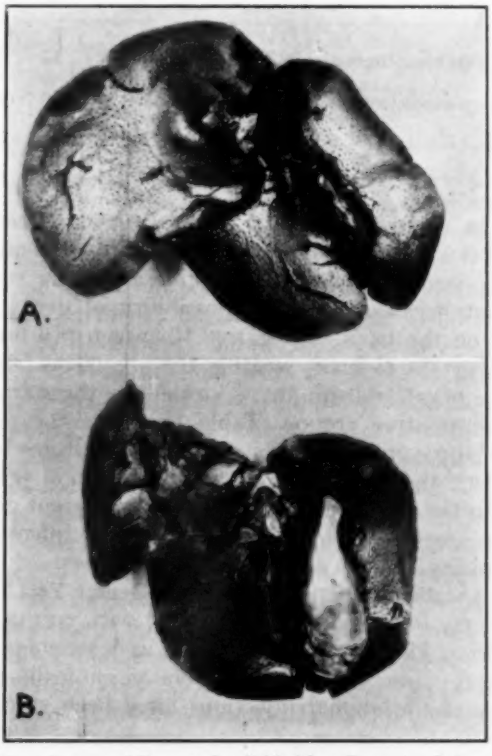

FIG. 10.—*A*, normal liver and gall bladder; *B*, acute cholecystitis.

the brain. Occasionally multiple cortical hemorrhages were seen (Fig. 9, *A*).

Rarely hemorrhages were found in the cord or sciatic nerves (Fig. 9, *B*).

Miscellaneous. Acute splenic tumor was common. Occasionally infarcts of the spleen were present. Once an acute cholecystitis (Fig. 10, *B*) was found. Little attention was paid to other types of gall bladder lesions because of the frequent occurrence of coccidiosis in the animals used. Other lesions observed were tenosynovitis, lymphadenitis, onychia, thyroiditis, hemorrhagic colitis and hemorrhages in the skin.

TABLE II.—LESIONS IN RABBITS FOLLOWING THE INJECTION OF BACTERIA FROM DIFFERENT ROENTGENOGRAPHIC GROUPS OF TEETH.

Group.	No. of animals.	No. of patients.	Percentage of animals showing lesions.							
			Joint.	Kidney.	Muscle.	Endocardium.	Myocardium.	Brain.	Eye.	Stomach and duodenum.
Roentgenographic negative teeth	232	89	59	36	24	17	9	3	13	7
Roentgenologic positive teeth .	224	93	63	34	22	16	12	5	13	16
Areas of residual infection . .	100	50	46	26	11	11	6	2	10	13

Lesions in Animals Injected with Different Roentgenographic Groups of Teeth. We have found that a high percentage of roentgenographic negative pulpless teeth give a positive culture.[4] This is important because often the possibility of dental infection is eliminated on the basis of negative Roentgen ray findings. It is equally important to know whether the organisms from the roentgenographic negative teeth are as virulent as those from the roentgenographic positive group. Table II shows the results of the injection of three groups of animals with the cultures from different types of teeth and from areas of residual infection. There is little difference in the incidence of lesions in the different groups, except that those injected from the areas of residual infection showed a lower morbidity.

Elective Localization of Bacteria from Dental Foci. Three hundred and forty-five rabbits were injected with cultures of patients suffering from kidney infection, heart and vascular disease, eye infection and peptic ulcer. These were all clinically proven cases. The results of the animal injections have been studied from the

standpoint of elective localization and reported in detail elsewhere.[5, 6, 7, 8]

TABLE III.—ELECTIVE LOCALIZATION OF BACTERIA FROM DENTAL FOCI OF INFECTION.

Cultures from patients with	No. of animals.	No. of patients.	Percentage of animals showing lesions.							
			Joint.	Kidney.	Muscle.	Endocardium.	Myocardium.	Brain.	Eye.	Stomach and duodenum.
Kidney infection	48	10	73	85	25	4	4	2	6	6
Heart and vascular disease	46	11	72	30	22	57	37	2	4	13
Eye infection	142	30	56	33	18	14	10	9	65	6
Peptic ulcer	109	25	53	23	29	14	12	2	5	57
No known kidney, eye, heart or gastric disease	1155	425	57	28	20	17	9	4	9	13
Total	1500	501								

In Table III is shown the incidence of involvement of the different organs of the rabbit after inoculation with bacteria recovered from foci in different clinical groups of patients. The animals injected with bacteria from patients suffering from kidney disease had involvement of the kidneys in 85 per cent, while only 23 to 33 per cent of the other groups showed kidney disease. Fifty-seven per cent of the rabbits injected with the cultures from patients having clinical evidence of heart or vascular disease showed lesions in the endocardium and 37 per cent in the myocardium. Of the other groups, involvement of the endocardium occurred in 4 to 17 per cent, and of the myocardium in 4 to 12 per cent. One hundred and ten rabbits were injected with cultures from patients suffering from metastatic eye infection. Of these 65 per cent showed infection of the eye. The incidence in the other groups varied from 5 to 9 per cent. In the rabbits injected with bacteria recovered from foci in patients having peptic ulcer 57 per cent showed gross lesions in the stomach or duodenum or both. The incidence of similar lesions in the control groups varied from 6 to 13 per cent. It will be noted that often more than one organ is involved. It is likewise

exceedingly common to find in patients more than one systemic disease of focal origin.

Summary and Conclusions. A study is reported of the lesions in 1500 rabbits following the intravenous injection of bacteria from chronic dental infection.

Lesions of various organs were observed in a large percentage of the animals injected.

The incidence of lesions in animals after the intravenous injection of bacteria agrees quite closely with the lesions due to chronic focal infection as observed in man.

Organisms recovered from roentgenographic negative teeth are as pathogenic for rabbits as those cultures from roentgenographic positive teeth.

Bacteria from chronic foci, if etiologically related to systemic disease, tend to reproduce in animals the lesions from which the patient suffers.

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REVIEWS.

A Manual of Proctology. By T. Chittenden Hill, M.D., Instructor in Proctology, Harvard Graduate School of Medicine. Second edition. Pp. 294; 101 illustrations. Philadelphia and New York: Lea & Febiger, 1926. Price, $3.50.

The second edition of this manual has been carefully revised and in part rewritten. The keynote of the book is practicality. The text is succinct but explicit and there are many useful prescriptions included. Dr. Robert C. Coffey's noteworthy article upon "The Radical Operation for Cancer of the Rectum" is incorporated. Typographical errors are unfortunately rather numerous. The work will be useful to the general practitioner and general surgeon.

R. G.

Plastic Surgery of the Head, Face and Neck. By H. Lyons Hunt, M.D., L.R.C.S. (Edin.). Pp. 404; 342 engravings and 10 colored plates. Philadelphia: Lea & Febiger, 1926. Price, $7.00.

It is only within the last few years that plastic surgery has been considered in the light of surgery alone. The first report of plastic surgery was in the year 2000 B.C. Many long years intervened between that and the remarkable advance that has come as a result of the World War. It is not a new art, but the results obtained have increased so enormously during the last few years that little will be credited to the previous thousands of years. Plastic surgery has taken its place as a real and much needed branch of the treatment of human ills.

The author has endeavored to present the subject in its entirety. Special chapters are devoted to the general consideration of the skin and its appendages, local anesthesia, grafts and transplants, wounds, congenital superficial defects and reports of various defects of the scalp, face and neck. In each chapter the anatomy of the part to be considered is outlined in detail. This renders the study of the proposed operation much easier to the surgeon considering it.

In the chapter, General Considerations, the author makes a statement that of 700 plastic operations he has had but 2 cases in

which the wound failed to heal by first intention. This I think is sufficient recommendation, and all of his readers could take a lesson from his technique outlined in this work. The book is profusely illustrated and in this respect the reviewer has but one criticism, namely, that instruments illustrated mean but little to the reader. In all other respects the illustrations have been admirably chosen, not only to show the technique before and after, but also the results after the operation has been completed.

The limited field chosen by the author has been most thoroughly covered and presented in a very interesting manner. E. E.

MODERN VIEWS ON DIGESTION AND GASTRIC DISEASE. By HUGH MACLEAN, M.D., D.Sc., M.R.C.P., Professor of Medicine, University of London, and Director of the Medical Clinic, St. Thomas' Hospital; Honorary Consulting Physician to the Ministry of Pensions; Consulting Chemical Pathologist to St. Thomas' Hospital. Pp. 170; 14 charts and 23 figures. New York: Paul B. Hoeber, Inc., 1925. Price, $4.00.

THIS book deals with the newer gastric physiology and pathology, laying especial emphasis on the significance of duodenal regurgitation into the stomach. In the diagnosis of gastric cancer the author attributes great importance to the presence of lactic acid in the stomach contents, and claims that it is often mistaken for hydrochloric acid, whereas the latter acid occurs in only a very small proportion of such cases. As a whole the work is very readable and stimulating. T. M.

THE DUODENAL TUBE AND ITS POSSIBILITIES. By MAX EINHORN, M.D., Professor of Medicine at the New York Post-Graduate Medical School; Visiting Physician to the Lenox Hill Hospital, New York. Second edition, revised and enlarged. Pp. 206; 121 illustrations, including 5 charts and 1 color plate. Philadelphia: F. A. Davis Company, 1926. Price, $3.00.

IN this second edition of his book on the duodenal tube Einhorn has included a review of the newer investigations which have been made possible by his introduction, in 1909, of an original method of sampling the duodenal and intestinal contents. While others have engaged extensively in this research, he himself has continued year by year to add important contributions to the literature of the subject and it is perhaps justifiable that his own results are given chief emphasis in this work. T. M.

THE SURGERY OF GASTRODUODENAL ULCERATION. By CHARLES A. PANNETT, D.Sc., M.D. (LOND.), F.R.C.S. (ENG.), Professor of Surgery in the University of London. Pp. 154; 55 illustrations. London: Oxford Medical Publications, 1926.

THIS interesting and well-written monograph will be found valuable to the surgeon chiefly because it brings within the covers of a short volume a résumé of most of the recent pertinent contributions to the literature of the subject from the great clinics of Europe and America. These have been collected with discretion and evaluated with judicious impartiality. Emphasis is placed upon the indications for and the choice of various operative procedures, and the present trend toward the more extensive resections is reflected. Despite its brevity the work is comprehensive, and illuminates a subject which is a source of active surgical controversy.

R. G.

SURGERY OF NEOPLASTIC DISEASES BY ELECTROTHERMIC METHODS. By GEORGE A. WYETH, M.D. Pp. 316; 137 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $7.50.

THIS book contains ten chapters dealing with the terminology, history and production of high-frequency currents. It is an excellent description of the different types of endothermy and the endotherm knife, with suitable description of the use of these agents in the treatment of both benign and malignant disease. The book is an excellent contribution to this field of endeavor and should be welcomed by both beginners and pioneers in this type of work. The author is to be congratulated on his very clear presentation of this subject, and the publisher is to be commended on the very readable type and splendid illustrations.

E. P.

RADIOTHERAPY IN RELATION TO GENERAL MEDICINE. By FRANCIS HERNAMAN-JOHNSON, Radiologist to French Hospital, London. Pp. 211. London: Humphrey Milford, Oxford University Press, 1926.

THE first chapter of this book covers the physics of radiation very well and is well written, clear and short. The tendency of the author is to view the radiotherapy of malignancy through rose-tinted glasses. That malignant cells are inhibited or killed, and the body defenses strengthened by the proper wave length or frequency of vibration of radiant energy, is the foundation upon which a magnificent superstructure seems to be ill-advisedly laid.

P. S.

THE BACTERIOPHAGE AND ITS BEHAVIOR. By F. D'HERELLE, M.D., Director du Service Bacteriologique du Conseil Sanitaire Maritime et Quarantenaire d'Egypte. Translated by GEORGE H. SMITH, PH.D., Associate Professor of Bacteriology and Immunology, School of Medicine, Yale University. Pp. 629; 6 illustrations; numerous tables and charts. Baltimore: Williams & Wilkins Co., 1926. Price, $8.00.

THE first collected work of the author was published in 1921. Its English translation appeared in 1923. Since these publications a great number of articles dealing with the bacteriophage have appeared. The inclusion of this work in the current collection presents a volume more than double the size of the first publication. A bibliography of 647 references is an important feature.

Part I considers the phenomenon of bacteriophagy; Part II, the nature of the bacteriophage; Part III deals with the behavior of the bacteriophage in contact with a parasitic bacterium in the higher animal or vegetable organism. This latter brings into consideration the practical application of the bacteriophage as a therapeutic agent in disease. The progress along this line has been disappointing. J. S.

THE SURGICAL TREATMENT OF GOITER. By WILLARD BARTLETT, A.B., A.M., M.D., D.SC., F.A.C.S. Pp. 358; 130 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $8.50.

THE subject presented in this book conforms well to its title. The more theoretical phases of etiology, development, thyrotoxicosis, etc., have been entirely disregarded and the author has apparently kept constantly before him the necessity of presenting the problem of diagnosis, prognosis and treatment in a practical manner to the surgeon. It is pleasing to note that the necessity of coöperation between the pathologist, internist and surgeon is emphasized. The chapters on pathology and the "goiter heart" are worthy of especial notice. Likewise, the method of presenting operative indications, by quoting from various men well known on the subject of "goiter surgery," instead of setting down dogmatic rules which might be influenced by personal limitation, is to be commended.

As in all his monographs, the present work is full of details, particularly in regard to preoperative and postoperative treatment. The assumption, by a recognized authority on this subject, that toxic goiter patients demand more intensive preoperative and postoperative care than any other surgical group of cases, is well founded and conforms to the opinion, I think, of all clinics where goiter surgery is done. F. G.

ELEMENTS OF PATHOLOGY. By ALLER G. ELLIS, M.Sc., M.D., Rockefeller Foundation Visiting Professor of Pathology and Director of Studies, Medical Department of Chulalongkorn University, Bangkok, Siam; one-time Associate Professor of Pathology, Jefferson Medical College, Philadelphia. First edition. Pp. 544; 95 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $5.00.

THIS is a book that will be received gladly by teachers of pathology. It is, as its name indicates, an elementary book dealing with facts; this, rather than a disquisition on probabilities which we ourselves believe today and deny tomorrow.

In the first part Dr. Ellis presents, in a simple way, the well-known pathological processes, discussing their cause, pathogenesis and effects.

The chapter devoted to tumors is too brief. There should be a more extensive description of their gross and microscopic appearance.

The manner in which the author presents "special pathology" and postmortem technique in Part II is most pleasing. While outlining the method for removing organs and examining them, he describes the more common lesions, linking the histologic structure with the gross anatomy.

An excellent though brief description of methods for preserving gross specimens, and for the preparation of tissue for microscopic study, is to be found in the last chapter.

Considered as a whole, the work is an excellent handbook for the student or the practitioner. One may know by reading the preface that the author does not offer it as a text for the advanced students of pathology or as a guide to the pathologist. I would rather have a student study such a book, and supplement it with selected collateral reading, than to pore in a confused manner over the more generally accepted texts of theorists. F. K.

CHEMISTRY AND RECENT PROGRESS IN MEDICINE. By JULIUS STIEGLITZ, University of Chicago. Pp. 62. Baltimore: The Williams & Wilkins Co., 1926.

THE content of this book is the 1924 Charles E. Dohme Memorial Lecture of the School of Medicine of the Johns Hopkins University. It is an excellent review of the recent advances in medicine through the field of chemistry. It is from a chemist's viewpoint and perhaps rather more optimistic than the medical man would concede. The latter half of the lecture is concerned with modern work in the acid-base balance of the body and systems of oxidation-reduction potentials. W. K.

BOOKS RECEIVED.

Abstracts of Theses. The University of Chicago Science Series, 1923–1924. Pp. 396. Chicago: University of Chicago Press, 1926.

Histological Technique. By H. M. CARLETON, M.A., B.Sc., D.PH. Pp. 398; 17 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $5.00.

The X-Ray in Embryology and Obstetrics. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S. and MAXIMILIAN JOHN HUBENY, M.D., F.A.C.R., F.A.C.P. Pp. 420, 259 illustrations. St. Paul, Minnesota: Bruce Publishing Company, 1926. Price, $10.00.

Obstetrics. By JOHN S. FAIRBAIRN, M.A., B.M., B.CH. (OXON.), F.R.C.P. (LOND.), F.R.C.S. (ENG.). Pp. 221, 29 illustrations. New York: Oxford University Press American Branch, 1926. Price, $1.75.

The Pathology and Treatment of Diabetes Mellitus. By GEORGE GRAHAM. Second edition. Pp. 230. New York: Oxford University Press, American Branch, 1926. Price, $2.75.

Handbuch der Massage und Heilgymnastik. Band II. By DR. MED. FRANZ KIRCHBERG. Pp. 334, 23 illustrations. Leipzig: Georg Thieme, 1926.

Why Infections? By NICHOLAS KOPELOFF. Pp. 182, 16 illustrations. New York: Alfred A. Knopf, 1926.

Hydrogen Ion Concentration. VOL. I. PRINCIPLES OF THE THEORY. By LEONOR MICHAELIS, M.D. Translated by WILLIAM A. PERLZWEIG, M.A., PH.D. Second edition. Pp. 299, 32 illustrations. Baltimore: Williams & Wilkins Co., 1926. Price, $5.00.

The Ophthalmic Year Book. VOL. XXII. Edited by WILLIAM H. CRISP. Pp. 315, 9 illustrations. Chicago: Ophthalmic Publishing Company, 1926.

The Carrier Problem. By K. C. PAUL, M.B., B.S. Pp. 102, 1 illustration. New York: Oxford University Press, American Branch, 1926. Price, $1.75.

The Abdomen in Labour. By NORMAN PORRITT, M.R.C.S., L.R.C.P. (LOND.). Pp. 76, 29 illustrations. New York: Oxford University Press American Branch, 1926. Price $1.75.

Modern Clinical Syphilology. By JOHN H. STOKES, M.D. Pp. 1444, 885 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $12.00.

Diseases of the Ear. By HUNTER TOX. Revised and largely rewritten by GEORGE C. CATHCART, M.A., M.D. Second edition. Pp. 333, 87 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $3.50.

Enzymes. By SELMAN A. WAKSMAN and WILBURT C. DAVISON. Pp. 364. Baltimore: Williams & Wilkins Co., 1926. Price, $5.50.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and their Relationship.—GRINKER (*Arch. Int. Med.*, 1926, **38**, 292) presents evidence which makes him advance the opinion that normal gastric acidity may be present in pernicious anemia. He believes, furthermore, that the achylia which does occur in pernicious anemia is not a predisposing cause of the condition. He bases his contention largely on 3 cases which occurred in the Cook County and the Wesley Memorial Hospital, in which there was found free hydrochloric acid in the gastric analysis. The anemia in these cases was characterized by high-color index, megaloblasts and in 1 patient the symptoms of cord degeneration. It would appear from the very brief case reports which he has presented that the diagnosis of pernicious anemia might well be questioned, particularly so when hematologists at the present time very generally accept the absence of free hydrochloric acid in the gastric contents as one of the necessary symptoms which go to make up the symptom complex of pernicious anemia.

A Simple, Rapid Precipitin Test for the Diagnosis of Syphilis.—Gradually the Kahn test is being recognized throughout the country. This precipitin test is very generally gaining recognition as a test, which is comparable in many ways to the Wassermann and at the same time is reliable. BUTLER (*New Orleans Med. and Surg. J.*, 1926, **79**, 105), as the result of a study, in which he was comparing the blood-serum reactions with the several methods of testing, has developed a very accurate

slide test for syphilis, which is particularly available because of its simplicity. The test is done with a minimum amount of trouble in a very short period of time and there is no difficulty in reading the result. Butler employs for his antigen fresh baby veal hearts, which are treated by a simple technique and subsequently cholesterized. The antigen and the serum to be tested are placed upon a slide and thoroughly mixed. A characteristic granular precipitate appears if the serum is positive, while if no precipitate appears within two minutes the serum is negative. He gives the result of 500 sera, contrasting the Wassermann, Kahn and slide test. The results are magnificently comparable.

Experimental Intestinal Obstruction.—In a series of four papers HADEN and ORR (*J. Exper. Med.*, 1926, **44**, 419) deal with the chemical and blood changes which occur in the dog after obstruction of the upper gastro-intestinal tract. They show that there is a rapid and marked rise in the viscosity of the whole blood, with some increase in the viscosity of the plasma; that there is no more change in the surface tension; that there is a marked diminution in the sedimentation time of the red cells; that there is a marked fall of the chlorid content of the liver and a slight fall in muscle.

The Dwight-Frost Cardiorespiratory Test as an Aid in the Early Recognition of Myocardial Insufficiency.—One of the difficulties that the clinician has in his daily practice is to determine the efficiency of the cardiac musculature in patients presenting questionable signs and symptoms of cardiac disease. Numerous functional tests have been evolved which have been extensively advocated and widely tried, only to fall by the wayside on account of error in the principle upon which the test was based or difficulty in carrying out such a test. Several years ago a method was brought out by Frost, which depends upon variations of the pulse rate and blood pressure after marked increase of intrathoracic pressure. EUSTIS (*Southern Med. J.*, 1926, **19**, 585) confirms the statements that have been made by Frost as to the value of his test. He has used the test in a series of 100 patients with symptoms of cardiac disease and 100 individuals who were apparently normal. He believes that the test is of considerable value in arriving at the conclusion that the heart muscle is normal or diseased.

Experimental Glomerulonephritis Induced in Rabbits with the Endotoxic Principle of Streptococcus Scarlatinæ.—It has been estimated by those who have been working in scarlet fever, more particularly from the immunologic standpoint, that the causative streptococcus yields a definite exotoxin. This theory has been advanced largely by Dochez and his coworkers. DUVAL and HIBBARD (*J. Exper. Med.*, 1926, **44**, 567) have picked up the problem from a somewhat different point of view and with a different technique than has been employed previously in the study of the toxicity of Streptococcus scarlatinæ. They injected pure cultures of streptococcus into the belly cavity of a rabbit made immune by injections of homologous immune serum. Two to three hours after the injection this fluid from the peritoneal cavity was collected and filtered through a Berkefeld

filter. This material was sterile. When injected into the rabbit it gave the characteristic picture which we assume to be present in scarlet fever of the lower animals. They have thus shown that the toxin of scarlet fever is an endotoxin, because the lysate which was injected into the experimental animal consisted entirely of material broken down by the body lysins of the injected animal. This work was controlled further by injecting scarlatina streptococci into rabbits and by injecting culture filtrate into the animals, the culture filtrate producing none of the effects of the disease, showing that it contains no toxic principle. One of the most interesting developments of this study was the constant occurrence of acute glomerulonephritis after the intravenous injection of streptococcal lysate. This glomerulonephritis is analogous in every way to the nephritis which is found in individuals who die as a result of this complication of scarlet fever. Of particular importance is the fact that for the first time a type of experimental nephritis has been produced by what may be called the natural agent, that is, an agent which consistently causes nephritis in human beings. Studies that have been made in the acute forms of nephritis are dependent upon the use of salts of the heavy metals which are irritating to the kidneys, and while a picture has been developed which shows the pathologic changes which take place in acute nephritis, yet this picture has been produced by the agency of vehicles with which the human seldom if ever comes into contact.

SURGERY

UNDER THE CHARGE OF

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How to Diagnose and Treat Central Bone Lesions.—BLOODGOOD (*J. of Bone and Joint Surg.*, 1926, **8**, 471) writes that sarcoma as a central bone lesion is rare, and up to the present time it is a question as to a positive five-year cure after amputation. The author notes that even today there are surgeons and pathologists who seem unable or unwilling to look upon the giant-cell tumor as a benign pathologic process. Restudy of central lesions diagnosed chondrosarcomas has shown that the histologic picture was that of chondroma. This group with the giant-cell tumors compose a large number of the cases registered with Codman as five-year cures after amputation. Sarcomas which have evidently arisen in preëxisting chondromas or myxomas are the only proven types of central sarcoma in which the bone shell is intact. The pure myxomas may arise as central lesions, just as chondromas. The author feels that our greatest responsibility is not to make diagnosis

of malignancy in benign bone cysts or advise the unnecessary expense of Roentgen ray treatment, next not to allow a benign giant-cell tumor of the epiphysis to proceed to the thinning and destruction of the bone shell, because in this event curetting, although it may accomplish a cure with bone transplanting, will not preserve the same good function. Our next endeavor should be to recognize the possible and fortunately infrequent central chondrosarcomas or myxosarcoma, or the pure myxoma, so that we may explore under the protection of the cautery, recognize from the gross or frozen section and radically remove by resection or amputation.

Obstruction at the Vesical Outlet after Prostatectomy.—IRWIN (*Brit. Med. J.*, 1926, **2**, 3417) states that it is by no means uncommon for obstruction at the vesical outlet to recur after a short interval, however carefully and apparently successfully the operation has been performed and when there has been nothing to suggest malignancy. In obstructed cases patients complained of difficulty as their most prominent symptom before the prostatectomy. The enlargement was in each case of the smaller and more fibrous type, a fact which supports the usually held theory that postoperative obstruction is commoner in this class of case. The rapidity with which the wounds healed and the ease with which the patients subsequently passed water lead the author to believe that in dealing with postoperative obstruction it is advisable to tie a catheter into the bladder by the urethra, off and on, until the suprapubic wound is healed. While there is no doubt that the open operation as recommended by Sir John Thompson Walker is in the majority of cases to be preferred to the old "blind" method, cited cases prove that cicatricial contraction may cause obstruction and difficult micturition, even after the more thorough procedure.

Cholecystography.—WALKER (*Lancet*, 1926, **211**, 5366) claims that cholecystography is a new method of investigation of the biliary system based on the capability of the liver to excrete certain dyes opaque to the Roentgen rays. It is a means of studying the topographic anatomy of the gall bladder in the living. It throws light on the physiology of the gall bladder, on its activities under various conditions and on its multiple functions. It provides additional information in late and early stages of disease. This procedure is to the biliary system what the opaque meal is to the alimentary system and pyelography to the urinary tract. Oral administration never gives as good results as the intravenous method. It gives also far less information as regards function of the gall bladder, as the shadow appears much later, lasts a shorter time and is never as dense as that obtained by intravenous injection.

Acute Traumatic Craniocerebral Injuries.—MACLAIRE (*Ann. Surg.*, 1926, **83**, 741) writes that whether a fracture, aside from depressed fracture, is present or not is not of material consideration in the treatment of cerebral edema with or without intracranial hemorrhage or any other cerebral lesion. The presence of a linear fracture is a natural method of decompression and endeavors to prevent the development of cerebral compression. The relative value of the dehydrating agents

must now be given some attention. Magnesium sulphate in the concentrated solution advocated is the ideal of all the dehydrating fluids at our command. It can be administered either by rectum or mouth, with perfect safety and freedom from any of the dangers attending glucose and sodium chloride. Moreover, it does not have the disadvantageous feature of producing the initial rise in the intracranial pressure that all the intravenous solutions possess. In cases of nonprogressive hemorrhage associated with or without linear fractures of the vault or base of the skull, lumbar punctures with drainage should be given a trial for a few days if the condition of the patient does not warrant an immediate operation. In cerebral edema, either with or without hemorrhage, lumbar puncture may also be used with the same indications as described for hemorrhage. The subtemporal decompression still retains its undisputed value as a means of not only saving life and reducing cerebral edema, but also of restoring the injured to future normality. A bilateral subtemporal decompression must be performed in those cases where the brain fails to pulsate after one side has been operated upon and when the brain still continues to bulge in spite of the relief of pressure on one side. Suboccipital decompression is indicated in those instances where fractures of the posterior fossa exist with rapid forming medullary compression, associated with cerebellar signs. There are just two contraindications to operation and they are at the two extremes, shock and medullary edema. A helpful role to bear in mind, when in doubt as to the proper procedure to employ with the patient out of shock and not in medullary edema, is to perform a subtemporal decompression for the future welfare of the patient.

PEDIATRICS

UNDER THE CHARGE OF

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The Acquisition and Loss of Hypersensitiveness in Early Life.—STUART and FARNHAM (*Am. J. Dis. Child.*, 1926, **32**, 341) state the results of their investigations confirm the general impression that hypersensitiveness to food proteins is most commonly encountered in early childhood and that there is a general loss of sensitivity to these substances during childhood. They cannot predict, however, at what age such loss will occur. They could not find any case showing definitely the development of a specific food idiosyncrasy. They give figures showing the rarity of hypersensitiveness to inhalant proteins in infants. The number of cases, however, increase during the middle part of the first ten years of life. Instances are quoted that indicate that sensitiveness to specific inhalant proteins is developed. The inference is drawn that hypersensitivity to food proteins tends to be present at birth and to be gradually lost during childhood, whereas

hypersensitivity to inhalant proteins tends to be acquired and is more resistant to change. It can be seen from this that there is a changing state of sensitization to be expected during childhood and protein tests should be repeated at frequent intervals in order to obtain the best results with treatment. Excessive exposure to inhalant proteins, although they may show negative skin tests, should be avoided by the asthmatic child. The authors feel that active treatment by oral desensitization of subjects found to react to important food substances is preferable to waiting for the natural loss of such hypersensitivity.

Comparison of the Pirquet, Mantoux, Ring and Tubercumet Tests in Lymanhurst Children.—STEWART and COLLINS (*Am. J. Dis. Child.*, 1926, **32**, 367) publish these observations made on children admitted to the Lymanhurst Hospital for Tuberculous Children in Minneapolis. They found that in healthy children having negative tuberculin tests the ring and tubercumet tests are uniformly negative. In children not suffering from acute infections but having positive Pirquet and Mantoux tests associated with such clinical findings as enlargement and calcification of the bronchial lymph nodes, slight occasional elevations in temperature, under-nutrition and a history of exposure to tuberculosis, but with no clinically active tuberculosis, the ring and tubercumet tests were negative. Under such circumstances negative ring and tubercumet tests apparently are evidence that the tuberculous focus is inactive, and this information is of definite clinical value. In definitely active tuberculosis the ring and tubercumet tests usually are positive. Positive ring and tubercumet tests are not specific tests for active tuberculosis, for they may become temporarily positive as the result of active nontuberculous infections. To be of significance, the positive ring and tubercumet tests should be persistently positive. Under such circumstances when certain chronic nontuberculous infections, such as pyelocystitis, osteomyelitis and others are excluded, persistently positive ring and tubercumet tests should give the suspicion of the presence of active tuberculosis. A diagnosis of active tuberculosis on the basis of positive ring and tubercumet tests alone should never be made. In making a diagnosis of active tuberculosis the results of the ring and tubercumet tests should be used with, but not to the exclusion, of other established methods of examination. The ring and tubercumet reactions which are known to be positive in cases of active tuberculosis, but negative in healed tuberculosis are of undoubted value when other limitations are fully understood.

The Degree of Mental Deficiency Resulting from Congenital Syphilis.—DAYTON (*J. Am. Med. Assn.*, 1926, **87**, 907) believes that congenital syphilis is the cause of mental deficiency in only a few cases. He assumes that mental deficiency occurring with congenital syphilis is a result of the syphilis. He made a comparison to establish a satisfactory standard by comparing the mental grades occurring with congenital syphilis with a group of feeble-minded patients in whom the mental defects were due to other factors. In the patients having a Wassermann test there were 1956 negative, 68 positive and 21 doubtful reac-

tions. Seven patients with acquired syphilis and those in whom the reaction was doubtful were not included in the tabulations. Before a mental comparison could be made it was necessary to investigate the ages of the two groups, for if there were a preponderance of any particular age group in the positive cases a corresponding disproportion in the mental ages might result. The first comparison between the negative and positive groups was by chronologic ages, and it shows that in this respect there is little variations. As a further safeguard against the possibility of differences in the chronologic ages influencing the mental ages, the intelligence quotient of the individual cases was used in making mental comparison. There was a marked difference in the intelligence of the two groups. The positive cases showed fewer idiots, imbeciles and low-grade morons and more high-grade morons and borderline cases than the negative group. That is to say, the patients with congenital syphilis averaged higher in mental rating than those whose feeble mindedness was due to other causes. In spite of the lack of variation in ages in the two groups, the observer felt that some of the patients of the lower grade might have died in early years and left only those of the higher grade, but the school in which these observations were made accepts children as young as two years, and a review of the deaths in this institution would reveal any preponderance in the lower grade cases showing syphilis. Over a seventeen-year period in 228 deaths there were only 2 patients with a positive Wassermann reaction, and 1 died at the age of twenty-three years and the other at the age of fifty-seven years; 1 was a high-grade imbecile and the other a moron, so that the exception in the above cannot be said to have any evidence in favor of its occurring.

Vomiting in Infants.—GREER (*J. Am. Med. Assn.*, 1926, **87**, 936) reminds us that congenital hypertrophic pyloric stenosis presents almost an unmistakable picture. There is a fulminating progression of the vomiting, constant and clearly defined epigastric peristaltic waves and almost invariable resistance to medical and dietary therapy. The palpation of the pyloric tumor is not at all essential to the diagnosis, and its presence does not necessarily establish the diagnosis. Roentgen ray study only assists in the way of corroboration. He states that he has never seen an instance of so-called mild hypertrophic pyloric stenosis, nor has he ever been successful in curing pyloric vomiting by medical and dietary means in any case in which the diagnosis of congenital hypertrophic pyloric stenosis was not open to serious question. In comparing the two series of cases quoted in his article there seems to be little in common except that severe forceful vomiting occurred in both, and the second group showed a delayed passage of food through the pylorus. As a result of his experiences he urges early surgical intervention after the establishment of the diagnosis.

OBSTETRICS

UNDER THE CHARGE OF

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Abruptio Placentæ.—The accidental hemorrhage is taken up from all angles and the percentage of separation of a large number of cases is tabulated by MAGWOOD (*Canadian Med. Assn. J.*, 1926, **16**, 665). It is divided into four divisions: (*a*) Traumatic; (*b*) localized pathologic changes at the uteroplacental site; (*c*) systemic evidence of toxemia with pathologic changes in the kidney, uterus and placenta; (*d*) maternal systemic diseases. It takes up the mechanical factors which result in concealed and frank hemorrhage. It draws attention to the statement made by Holmes, that there is one pathognomonic sign invariably present in abruptio placentæ, being the expulsion of old clots and perhaps old blood with the child or placenta. The uterus may show firm hardness or even flaccidity. Shock is prominent, especially in those cases in which hemorrhage is large or concealed. Blood pressure and toxemia accompanying the hypertension are both carefully described. It differentiates between placenta previa and concealed accidental hemorrhage. The treatment is given in detail, both for the delivery of the patient and treatment of shock and hemorrhage. The article shows clearly the seriousness of this complication, and warns the physician to explain the seriousness of the situation to the family and points out the advisability of a consultant being called.

Results with the Watkins Interposition Operation in the Treatment of Prolapsus Uteri.—This operation so well known in the profession has stood the test of time remarkably well in the hands of many operators in various parts of the world. This article by BRADY (*Surg., Gynec. and Obst.*, 1926, **43**, 476) is only another tribute to the late Dr. Watkins' pioneer work in this complicated and not uncommon condition of prolapsus uteri. It is another series of cases by the author that show equally good results. There were a few failures or partial failures, and in a very small percentage it was necessary to perform a secondary operation. All the women were past the child-bearing period. As Dr. Watkins in his original article made the point very clear that vaginal fixation of the uterus should never be done on a woman in the child-bearing period unless at the same time the patient is sterilized. Follow-up records of the cases over some period of years only shows further that this operation is not only originally sound, but satisfactory results for the patient can be accomplished in the hands of a competent surgeon. The author emphasizes the fact that the end results

for the Watkins interposition operation are better than any operative procedure for this condition yet known.

Lipiodol as an Adjunct to Tubal Inflation in the Diagnosis of Sterility.—RANDALL (*Am. J. Obst. and Gynec.*, 1926, **12**, 326) gives his experience in the use of the substance lipiodol for use in the transuterine inflation of the Fallopian tubes. By its use one is able to determine with accuracy the patency of the tube. The method is a step forward and is based on the lines of the original method of Rubin. Instruction to the patient for the preparation, the physical and gynecologic examination necessary, along with the fertility study of the male are clearly outlined. The operation is described in detail, and the article is accompanied by roentgenographic illustrations which show clearly the value of the procedure and the excellent results obtained with lipiodol. The prognosis in such cases is much more clear cut and definite and the indications for operation are better outlined.

The Association of Congenital Diverticula of the Fallopian Tube with Tubal Pregnancy.—MCNALLEY (*Am. J. Obst. and Gynec.*, 1926, **12**, 303) sets forth by numerous diagrams and pathologic sections clear evidence that the diverticula of the Fallopian tube actually exists. In the number of cases reported of tubal pregnancy 83.3 per cent diverticula of the Fallopian tube were present in the tubal pregnancy. This is a very high percentage of malformation, and that in all probability it was directly responsible for the arrest of the ovum. Even in so small a series it seems reasonable to suppose the diverticula are more common in ectopic pregnancy than has been considered heretofore, and that they are an etiologic factor of considerable importance in the production of tubal pregnancy.

Injury of the Cervix Uteri and its Intermediate Repair.—WILLIAMS (*Am. J. Obst. and Gynec.*, 1926, **12**, 365) fully discusses the question of cervical laceration following delivery. A large number of cases were studied and worked upon which resulted in the finding that in 86 per cent of all the deliveries there occurred cervical lacerations; 85 per cent of all primiparæ had cervical injury. They subdivided the lacerations into three classes: (1) That which injures the mucous membranes only; (2) injuries that extend into the body of the uterus and to the angle of the fornix; (3) those lacerations which extend into the broad ligaments. Taken into consideration were the age of the patient, the pariety, the occipital presentations, the question as to whether the membranes were ruptured or unruptured, the length of time of labor, the sedatives, the kind of analgesia, the use of pituitrin, the instrumentation and size of baby. The operation for cervical repairi s done on the eighth or tenth day post partum and the author is convinced that intermediate repair of the cervix is the proper means of reducing much maternal morbidity. The technique of operation is fully described. The operation itself does not prolong the period of convalescence. The procedure properly fulfilled minimizes the occurrence of chronically infected cervix and endometritis and is considered in this article a definite prophylactic measure against the malignancy of the uterus.

GYNECOLOGY

UNDER THE CHARGE OF

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Cancer of the Parametrium.—In considering the extension of carcinomatous growth from its primary location in the cervix to the parametrial tissues, MARTIN and ROGERS (*Am. J. Roentgenol.*, 1926, **15**, 336) have found that the most distressing symptom encountered is a constant aching pain located deep in the groin and radiating down to the thigh, laterally to the hip, posteriorly to the sacroiliac and upward to the costovertebral angle. It may occur on one or both sides and is, they believe, in almost every instance due to partial or complete stricture of one or both ureters resulting from lateral malignant extension into the broad ligament areas. This lateral extension is of major importance because it finally brings about the death of the patient by occluding both ureters and producing uremia. Efficient therapy must, therefore, always be directed against this region as vigorously as against the primary growth. In considering this problem from its various angles, it has seemed apparent that the method adopted should depend largely on the tolerance of the ureter to radiation. For this reason, an attempt has been made to determine this tolerance in dogs. Five animals were treated in practically the same manner except that the time of irradiation was varied. Each dog received morphin (gr. $\frac{3}{4}$) and atropin (gr. $\frac{1}{100}$) hypodermically. The morphin was sometimes repeated during the experiment. About thirty minutes later 40 to 50 cc. of Grehant's solution, a mixture of alcohol and chloroform, was given by stomach tube, well diluted. This produced narcosis and muscular relaxation, lasting eight to ten hours. At times it was necessary to use small amounts of ether to produce a deeper anesthesia during the actual surgical procedures. The abdomen was shaved and prepared with iodin and alcohol. A left rectus incision was made and the intestines were packed into the right side of the abdomen, thereby exposing the left ureter. A 1-mm. brass capsule containing 50 mg. of radium in eight vanadium steel needles was placed against a lead shield 2 mm. thick, and the whole applicator was covered with rubber 1 mm. thick. This device was placed so that the radium capsule lay directly against the ureter while the lead shield separated it from the other abdominal contents. Several layers of gauze moistened in warm normal saline solution were placed over this applicator and two sutures were passed through the muscles of the back and tied so that they held the radium firmly against the ureter. In 2 animals the ureter lay in an inaccessible position, and it was necessary to open the parietal peritoneum and change its position before the applicator

could be placed. The irradiation was continued in the various animals for periods of two, three, four, five and six hours. In each animal the irradiated portion of the ureter had a white, anemic appearance, but showed no gross changes in size. Adhesions were present about the ureter in each irradiated region and were most extensive where the largest doses were used. However, these adhesions did not produce definite constriction of the ureter in any of the animals and no gross evidence of hydronephrosis could be observed. Pyelograms made after removal of the kidneys and ureters showed no gross changes except in the animals in which 2.5 erythema doses were used. In this instance there was a very slight dilatation of the left kidney pelvis, but this condition appeared to be due to surrounding adhesions rather than to a change in the ureter itself. These findings suggest that the ureter is more resistant than either the bladder or the rectum and will probably not be damaged when the broad ligaments are extensively treated with heavily filtered radiation.

Operation for Vesicovaginal Fistula.—The operative procedure for the cure of vesicovaginal fistula which is recommended by FREUND (*Zentralbl. f. Gynäk.*, 1926, **50**, 1177) is based on the principle of the Bassini herniorrhaphy. In this operation a large horseshoe-shaped incision is made in the vaginal wall surrounding the fistula with the base below. The flap included in the incision is dissected downward, carrying the opening of the fistula with it. The opening in the underlying bladder is then sutured with interrupted stitches, after which the free edge of the denudation (between the fistula and the urethra) is sutured to the base of the flap which is temporarily retracted down ward, the suture only including the deeper layers of the under surface of this flap and not going through to the mucous membrane. When this suture is completed the sutures in the bladder have been entirely covered and the second suture lies in a higher plane. A new denudation is now made between this last suture line and the urethra corresponding in size and shape to the flap which had been originally dissected, and this flap is then drawn upward and carefully sutured to this new denudation. In this manner the bladder sutures are covered by two layers of vaginal tissue and none of the three suture lines are superimposed. This seems to be a rather ingenious operation, but could probably only be applied to those cases in which the fistula lies in the lower part of the vagina and is readily accessible.

Irradiation of Cancer of the Fundus.—DÖDERLEIN (*Zentralbl. f. Gynäk.*, 1926, **50**, 847) reminds us that carcinoma of the fundus is a different disease, biologically, clinically as well as anatomically from cervical cancer. Since its histologic structure is usually that of adenocarcinoma, it does not so readily break into the surrounding tissues and, furthermore, it is not surrounded by tissues rich in lymphatics as in cervical cancer, so that it takes a much longer time before it becomes adherent to neighboring organs. Clinical observation shows that fundal cancer occurs at a later time of life and grows more slowly than cervical cancer. In reviewing his clinical material, he found that of 75 cases of cancer of the fundus treated by irradiation, 27 (36 per cent) were alive five years after the end of the treatment. In a previous

report he had shown an absolute curability of 58.8 per cent in cases treated by operation, but this figure cannot fairly be compared with the 36 per cent curability by irradiation because the types of cases in the two series were not alike. In the operative group the operability was only 51 per cent. After a discussion of his results, he comes to the conclusion that with a proper selection of patients the results of irradiation in fundal cancer will be just as good as those of operation, which is in contradiction to the opinion which he formerly expressed. His technique consists of the intrauterine application of 100 mg. radium bromide for twenty-four hours, repeated two or three times at six-week intervals, supplemented by Roentgen irradiation of the pituitary gland and the abdomen.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Relation of Paranasal Sinus Infection to Disease of the Lower Respiratory Tract.—"There is abundant clinical and some experimental evidence in support of the statement that certain types of diseases of the paranasal sinuses tend to produce peribronchial infections, with resultant chronic bronchitis, asthma and bronchiectasis." In order to identify the lymph channels that drain the sinuses, MULLEN (*J. Am. Med. Assn.*, 1926, **87**, 739), in association with Ryder, injected suspensions of India ink into the maxillary sinuses of etherized rabbits and into the frontal sinuses of etherized cats. Similar results were obtained from all the experiments. By tracing the carbon deposits, it was found that the lymphatic absorption from the paranasal sinuses was by way of the submaxillary and internal jugular nodes, the lymph ducts, the great veins, the right side of heart and the lungs. Moreover, the bronchial and mediastinal glands were involved, too. When infectious material was introduced into the sinuses the infections were found to follow the same route. In no instance were the faucial tonsils affected. It was learned that infection from the sinuses often drains into the "tonsillar gland," a node lying beneath the posterior belly of the digastric muscle. After a discussion of the various pathologic types of sinusitis, the author says that "The hyperplastic is far the most important form of paranasal sinus infection as a factor in the causation of chronic chest infections." The three types of pulmonary infection that may be caused by paranasal sinusitis are acute bronchitis, bronchial asthma, chronic bronchitis and bronchiectasis. He believes that the association of sinus disease with bronchiectasis is far too common to be accidental, and stresses the early recognition and treatment of sinusitis in children.

Is a Differential Diagnosis between Middle and Internal Ear Deafness Possible?—"The helpful treatment of a given disability is dependent on a fundamental understanding of its causes and in the physical and chemical adaptation of the individual to its results. The greater part of the failure in the investigation of the sound-transmitting apparatus has been due to the limited number of tools available for such research. The electrical audiometer has given us a quantitative method of determinating minimum audition, and within the past five years has yielded much information. Otologists have built up a number of tests based on the use of the tuning fork. Such tests, when associated with the spoken voice and the whisper, have been employed in an attempt to locate the given impairment in hearing. Two types of deafness have been established, the conduction (middle ear) deafness and the perception (internal ear or nerve) deafness. Insofar as treatment is concerned, no great advance has been made since the invention of the Politzer bag. Insofar as prognosis is concerned, it seems to make but little difference whether the diagnosis is perception or conduction deafness. Chronic progressive deafness, therefore, presents not only a most pitiful condition, but is an open challenge for an extensive investigation of the problem—a problem directly connected not only with the happiness of many unfortunate individuals, but also one of tremendous economic importance." After extensive researches, employing the continuous scale audiometer, the authors have arrived at the conclusion that both bone and air transmitted sound normally enter the labyrinth through the oval window, bearing out the idea of Pohlman that the end organ is remarkably well insulated against all vibrations except those passing through the stapedial footplate. "The testing of air and bone transmission, therefore, resolves itself into a testing of the conduction system and does not in itself necessarily differentiate between a conduction and a perception deafness. The differential diagnosis between the two types of deafness may be empirically convenient and even time honored, but it is not necessarily correct." POHLMAN and KRANZ (*Laryngoscope*, 1926, **36**, 289) present additional evidence concerning the ranges of decreased acuity similar to the tone dead areas of Bezoldt. They report, with the aid of graphs, the audiometric findings of 7 individuals, the first 3 of whom showed actual deficiencies in their bone sensitivities in the middle part of the range, when tested with the bone activating telephone on the forehead. After a discussion of the significance of their observations, the author feel that this additional evidence substantiates their previous statement that both bone and air transmitted sounds normally enter the cochlea through the stapedial footplate; they "are inclined to doubt whether it is possible at the present time, and with the present methods, to definitely differentiate a perception from a conduction deafness."

Toothache Secondary to Otitis Media.—The association of otalgia with various affections of the teeth is well established. CASTERAN (*Rev. méd., Latin America*, 1926, **11**, 1225) has encountered several cases of middle-ear disease, in which odontalgia was the outstanding feature. The toothache disappeared after the aural condition was cured. In some cases paracentesis tympani relieved the pain immediately. The author explains the phenomenon on the decussation of the neural fibers in Arnold's ganglion.

RADIOLOGY

UNDER THE CHARGE OF

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The Effect on Tuberculosis of Bones and Joints of Food Exposed to Ultraviolet Radiation.—Numerous investigations having previously shown that food subjected to ultraviolet radiation has a favorable influence on rickets, PATTISON (*Brit. J. Rad.*, 1926, **31**, 65) has applied the method to the treatment of tuberculosis of the bones and joints in children. In his cases ½ pint of the usual 1½ pints of milk was exposed to the rays from a mercury-vapor lamp at a distance of 2 feet for half an hour daily. Roentgenograms of the patients made after two to six months shows marked improvement. The author notes that the usual local, general and dietetic treatment may have been a factor, but in all the cases except 2 the patients had already been treated for several months without striking improvement.

Additional Roentgen Ray Signs of Chronic Gastritis. — BASSLER (*Am. J. Roentgenol. and Rad. Therap.*, 1926, **15**, 323) feels convinced that there are Roentgen ray signs of simple and common forms of chronic gastritis, that while not always present, when they are, are pathognomonic. Routine postmortem examinations and study of sections prove this to be a common disorder. In well-established chronic gastritis fibrillary types of waves are seen along the greater curvature, only occasionally along the lesser curvature. This serration of the greater curvature outline may be localized, but more frequently involves the lower two-thirds of the greater curvature. This irregularity is noted only in the films or observations made in the prone position and is completely obliterated in those made in the upright. The whole stomach displays a lack of regular, large, sweeping peristaltic phenomena.

Roentgen Ray and Metastases in Breast Cancer.—COVENTRY (*Minnesota Med.*, 1926, **14**, 316) reviewed a series of 47 cases seen in a five-year period. Sixty per cent were dead, 10 per cent were living with recurrences and of the 30 per cent living the majority were operated in the last two-year period. A review of the literature showed the most unfavorable results were with the cases intensively rayed. The avenues of metastases are: (1) The axillary glands; (2) the clavicular chain of glands; (3) the chest wall and mediastinum; (4) the peritoneal cavity; (5) local recurrences in the skin; (6) the bony or skeletal parts. Ninety-five per cent of his series had axillary involvement before operation. Experience has taught that patients with metastases into the clavicular group of glands are inoperable. Roentgen

ray was most successful in preventing local recurrences in the skin and least successful in treatment of bone metastases; high-voltage doses will relieve pain in the latter group. With evidence of metastases operative procedure is contraindicated.

Problems in Diagnosis and Treatment of Metastatic Tumors in the Chest.—That the treatment of metastatic tumors has not reached the stage of recognition and widespread approval which the diagnostic side has received, is the opinion of BUTLER and HABBE (*Radiology*, 1926, **6**, 400). With the ever-increasing knowledge of the cancer problem and broader empirical knowledge of the response to radiation, they feel entirely justified in treating selected cases of metastatic malignancies in the chest with the reasonable hope of positively benefiting the patient. Groups of cases are presented: (*a*) Not treated; (*b*) treated with questionable benefit; (*c*) cases treated and definitely benefited. Their conclusions are: (1) The majority of even well-advanced pulmonary metastatic cases will be still free of symptoms; (2) undoubted Roentgen ray evidence of metastatic malignancy established before operation may prevent unnecessary and even harmful operations; (3) all cases of metastatic malignancy in the chest are not suitable to radiation therapy, but when indications are favorable marked ameliorations of symptoms and temporary remission of the disease can usually be accomplished.

The Etiology and Treatment of Chronic Ulcerative Colitis.—BARGEN (*Am. J. Roentgenol. and Rad. Therapy*, 1926, **16**, 10) from recent experimental work has formulated two conceptions of this disease: (1) The disease is of infectious origin; (2) the infection is conveyed by repeated "showers" of bacteria being thrown into the circulation by a distant focus. The clinical story, the proctoscopic and roentgenologic pictures, the gross and microscopic appearance, many of the complications and the experimental evidence substantiate these hypotheses most convincingly. A Gram-positive, lancet-shaped diplococcus has been isolated in the majority of cases; he believes, if searched for at the proper time, it would be found in all. Acute exacerbations of bloody diarrhea have been seen repeatedly after the removal of septic tonsils or periapically infected teeth which subsided with the healing of the abrasion made where the focus was removed. In 1 patient a suppurative cholecystitis was seemingly the focus. An important step in the treatment is the removal of these distant foci of infection, after which the treatment consists in immunization against the organism. The subcutaneous administration of vaccines and vaccine filtrates from the diplococcus, prepared by the methods of Rosenow forms the main portion of the treatment. Of 178 patients thus treated only 7 have come to surgery in the past two years. Seventy-eight have been well from several months up to two years; 6 have died; 4 were not benefited; the remainder had not been heard from for several months and it seems reasonable that some of these were well. Three cases were reported in detail.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Löwenstein Method for Isolating Tubercle Bacillus from Sputum.—Passos (*Compt. rend. Soc. de biol.*, 1925, **93**, 1552) has been successful in isolating tubercle bacillus from 104 sputums which showed the bacillus in direct smear by the Ziehl-Neelsen staining method. He also isolated it twice from 33 sputums which were negative by direct smear. He tested 5 of the isolated cultures on guinea pigs. The technique used was a modification of Löwenstein's (*Wien. klin. Wchnschr.*, 1924, **37**, 231) and was briefly as follows: The specimen of sputum was put in a centrifuge tube to which was added five times its volume of a 15 per cent sulphuric-acid solution, thoroughly shaken for twenty minutes and then centrifuged at high speed for fifteen minutes. The precipitate was washed with physiologic saline and centrifuged three times. The last precipitate in a few drops of saline was seeded on five tubes of glycerinated potato and the plugs paraffined and incubated at 37° C.

Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother.—A case is reported by Gray and Feemster (*Arch. Path.*, 1926, **1**, 348) in which the pancreas of a newborn child of a diabetic mother contained approximately twenty-four times as much insular tissue as the normal pancreas. The mother had been diabetic for ten years, and showed a high blood sugar repeatedly. In the fourth month of the gestation she excreted 14 gm. of sugar a day on a diet of 1800 calories with 30 units of insulin. During the last month of her pregnancy she was sugar-free on a diet of 2225 calories with only 15 units of insulin daily. Following delivery, there was a rapid rise in blood sugar from 0.096 to 0.225 mg. per 100 cc. of blood. The baby showed a low blood sugar, 0.067 mg., on the third day, with a possibility of a more marked hypoglycemia before death. The increase in the maternal blood sugar is suggested as the stimulus which called forth the increase in insular tissue in the pancreas of the child. This resulted in a decrease in the maternal blood sugar until delivery, when it suddenly rose. Hypoglycemia, the result of this insular hypertrophy and hyperplasia, may have played a role in the sudden death of the baby. Associated with the hypertrophy of the islands of Langerhans was a hypertrophy of many medullary cells in the suprarenals.

Döderlein's Vaginal Bacillus.—It is a long time since Döderlein (Scheidensekret, 1892) published his studies on the bacteria of the vagina. The recent work of LASH and KAFLAN (*J. Infect. Dis.*, 1926, **38**, 333) on the bacillus of Döderlein is based on the definition of that organism as given by him, that is, a long, thick, nonmotile, Gram-positive anaërobic, facultative aërobic bacillus, forming dew-drop colonies on solid media. They chose for this study women approaching the term of their pregnancy as the source of their material, since, according to Apel, they would expect to find the vaginal bacillus in 50 per cent of such cases. On direct smear 42 per cent showed this organism, while only 13 per cent were successfully cultured, using both aërobic and anaërobic methods. Because of the high acid-forming character of this bacillus, these authors compared it by cultural methods with Bacillus acidophilus, and found that the Döderlein bacillus could be subgrouped into four strains, which classification was further supported by agglutination, precipitin and complement-fixation tests. The definition given above applied to the group, but in addition it was found that milk is coagulated by all but one strain and that all reduce nitrates to nitrites. The most favorable medium was found to be neutral 1 per cent lactose broth. The other organisms found in the secretions most frequently were Staphylococcus albus, diphtheroids, yeasts and Streptococcus viridans. These were found to be less pathogenic than the same bacteria as found in the pharynx. The authors support the hypothesis of Döderlein, that this bacillus has an inhibitive action on the growth of other organisms in the vagina.

The Relation of Thrombocytes to Hemorrhagic Diathesis.—The clinical study of blood platelets has been rapidly progressing, especially in diseases of the hematopoietic system. It would seem that they are increased in secondary anemias, chlorosis, polycythemia rubra and at times in lymphatic leukemia, but are very greatly reduced in certain other conditions, notably those in which hemorrhages, petechiæ, etc., are factors. HELD (*Arch. Int. Med.*, 1926, **37**, 414) has published a review of the findings and differential diagnosis of Werlhoff's disease, essential thrombocytopenia or idiopathic purpura, as it has at different times been called. Briefly he found that the platelets are markedly decreased in this condition. Furthermore, the clots produced in the blood showed a lack of retractility and did not coagulate properly. Removal of the spleen resulted in a slight rise in the count and then a gradual return to the previous low level, but the condition improved. The spleen seems to affect the megakaryocytes of the bone marrow (which are the parent cells of the platelets) in some way to cause loss of their agglutinative and retraction power. It is possible the condition in idiopathic purpura is due to some unknown toxin working upon these cells. Symptomatic purpuras have very little lowering of their platelet count. Treatment of these conditions must as yet be symptomatic. Calcium salts have been extensively used in treatment, and transfusions have often proved of benefit. As yet the method of treatment has not advanced as far as the methods for diagnosis.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Observations of the Normal Bacterial Flora of Nose and Throat with Variations Occurring during Colds.—SHIBLEY, HANGER and DOCHEZ (*J. Exp. Med.*, 1926, **43**, 415) studied the normal bacterial flora of the nose and throat of 13 individuals over periods ranging from five to nine months. Observations were made of qualitative and quantitative changes in the flora occurring in the course of colds and of throat infections appearing in the group. The normal basic nasal flora includes Staphylococcus albus, diphtheroids, and for certain individuals Staphylococcus aureus and citreus. Occasional transient bacteria are Gram-negative cocci and nonhemolytic streptococci. The normal basic throat flora includes Gram-negative cocci, nonhemolytic streptococci and for certain individuals "large Gram-positive cocci," Bacillus influenzæ, Bacillus "X" and diphtheroids. Transient organisms are Staphylococcus albus, hemolytic streptococci, Staphylococcus aureus and citreus and pneumococci. No bacteria were found in early cold cultures to which a causative role could be assigned. In the course of colds the basic flora of the nose was often scanty in the early stages. The throat showed reduction of prominence or alterations in predominance of the basic flora. Certain organisms were prominent in colds, usually as late or secondary invaders; these included Staphylococcus aureus, hemolytic streptococci and Bacillus influenzæ. There was a striking increase in the incidence of hemolytic streptococci in throat infections.

Observations on 6500 Cases of Lobar Pneumonia at the Cook County Hospital, Chicago.—KELLY (*J. Infect. Dis.*, 1926, **38**, 24) states that in the seven and a half years, from January 1, 1917, to July 1, 1924, there were 6531 cases of lobar pneumonia at the Cook County Hospital, Chicago, with a case fatality of 36 per cent. The case fatality in the individual years varied between 34 and 41.4 per cent, with the exception of 1921, when only 26.6 per cent died. This decrease in 1921 occurred in both sexes, in negroes and whites and in all age groups. The death rate from this infection was markedly lower in the entire country in that year. The case fatality among the negroes was from 5 to 13 per cent below that of the whites in the different years. This was due to a lower case fatality in the negroes in the forty years and over group. The case incidence among the negroes in Chicago during this period was apparently twice that of the whites. The age inci-

dence in the 6531 cases showed a large number in the group under five years, the fewest in the second decennium, with a steady increase through the group forty to forty-nine years, followed by a decline so rapid that the number in the sixty-year and over group was very small. The case fatality was lowest in the five to nine group, and from that point increased proportionately with the age. The greatest number of persons with lobar pneumonia entering the hospital during the year was in the months of January through April. The lowest number was in August. The greatest case fatality was in October, the lowest in June, the variation throughout the composite year being from 32.4 to 41.8 per cent.

An Epidemiologic Study of Pneumonia and its Mode of Spread.—ROSENAU, FELTON and ATWATER (*Am. J. Hyg.*, 1926, **6**, 463) examined two groups of healthy persons in Boston to determine the distribution of the pneumococci. One group of 180 individuals had no known exposure to pneumonia, while the second group of 270 persons had been in contact with lobar pneumonia cases. The second, or contact group, carried a significant excess of fixed-type pneumococci over the controls, the excess being limited to those types (I and III) which were responsible for all of the 28 cases of pneumonia under study. The pneumococcus was found in normal throats of the control group with a frequency which in general confirms other studies of a similar nature, but it is pointed out that not one of the carriers could give a history of the source of his infection and all of the fifteen carriers of fixed-type organisms found in the control group were most probably infected from other carriers and not from cases. The frequency of fixed-type carriers among healthy persons is two to three times greater when the persons come into contact with cases of pneumonia. The findings suggest a tendency to lower average virulence among fixed-type pneumococci isolated from carriers than among fixed-type pneumococci isolated from cases. Type III pneumococcus was found among normal persons more frequently than Types I and II taken together. Yet Type III causes not more than one-sixth as much pneumonia in the United States as Types I and II cause. Type III apparently spreads from both carriers and cases more rapidly than does the Type I pneumococcus. This paradox in relationship probably depends on unrevealed factors of individual immunity to Type III pneumonia. The evidence presented corroborates the assumption that carriers as well as cases spread pneumococci. Both are productive sources of the parasite, the cases seemingly more prolific than the carriers. Comparison with data from other workers shows that technical procedures influence the results considerably, though in the main there is conformity in the findings when proper allowance is made for the differences in makeup of the groups studied. While these studies do not trace the entire series of events in the spread of lobar pneumonia, they define certain quantitative landmarks which make the epidemiology of the disease more clearly understandable.

PHYSIOLOGY.

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA.
SESSION OF OCTOBER 18, 1926.

The Kinetics of Exosmosis of Water from Living Cells.—MORTON MCCUTCHEON and BALDWIN LUCKE (from the Laboratory of Pathology, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole). In a previous communication, "The Kinetics of Osmosis in Living Cells," abstracted in this Journal (1926, **171**, 155), the authors presented data on the rate with which water enters the living cell (the unfertilized egg of the sea urchin) under the driving force of osmotic pressure. The present paper is concerned with the reverse process—exosmosis of water.

The response of cells to changes in osmotic pressure of the medium is believed to be an important adaptive mechanism. When the cell is placed in sea water diluted with distilled water—hypotonic solution—the cell swells, due to endosmosis of water, while conversely the cell shrinks in hypertonic solutions, due to exosmosis. The rate of swelling or shrinking can be determined by measuring the cells under the microscope at minute intervals. Since the cell is spherical, its volume can readily be calculated from its observed diameter, and thus the amount of water which enters or leaves the cell in a given time can be determined. It was found that in exosmosis as well as in endosmosis of water the rate of flow at any instant is proportional to the amount of water that must still pass the cell membrane before the cell reaches osmotic equilibrium with its surroundings. Expressed mathematically, we have $\frac{dx}{dt} = k\,(a-x)$ in which $\frac{dx}{dt}$ is the rate of osmosis, a is the total amount of water passing the membrane, x is the amount which has already passed at a time, t, and k is the velocity constant. In order to determine whether there is any difference in rate between endosmosis and exosmosis, cells were placed in 60 per cent sea water (that is, sea water, 60 parts; distilled water, 40 parts) and the values of k determined for several temperatures. Then the cells were put back in 100 per cent sea water (that is, sea water of full strength) and the constants for shrinking determined at the same temperatures. Under these conditions it was found that k had a much greater value in shrinking than in swelling, at corresponding temperatures.

Subsequent experiments showed that this difference was due not to any essential dissimilarity between exosmosis and endosmosis, but to the fact that the two processes had occurred in different concentrations of the medium—endosmosis in 60 per cent sea water and exosmosis in 100 per cent. When the two processes took place in solutions of the same osmotic pressure practically the same values of k were obtained.

This experiment was performed by first obtaining values of k for swelling in 60 per cent solution. Another lot of eggs were then allowed to swell in a more hypotonic solution—50 per cent—and after swelling was complete they were placed in 60 per cent sea water, in which they

shrank. The velocity constants for shrinking now agreed with those for swelling at the several temperatures. It follows from this and similar experiments that exosmosis and endosmosis are affected in the same way by temperature. The temperature coefficient in each case is high. As the result of these experiments, it is believed that there is no difference in the mechanism of exosmosis and endosmosis of water, except that the driving force of osmotic pressure is exerted in opposite directions in the two cases.

External Factors Influencing the Rate of Osmosis in Living Cells.—BALDWIN LUCKE and MORTON MCCUTCHEON (from the Laboratory of Pathology, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole). Of the external factors that affect the rate of osmosis in living cells, temperature has been discussed previously. The second factor, which is the subject of this communication, is the osmotic pressure of the medium. When the unfertilized sea-urchin egg is allowed to swell in hypotonic sea water or to shrink in hypertonic the rate has been found to be proportional to the amount of water which will pass the membrane before the cells reach osmotic equilibrium with the medium, or, $\frac{dx}{dt} = k\,(a-x)$, when a is the total volume of water entering or leaving the cell, x the amount that has already passed the membrane at time, t, and k is the velocity constant. The value of k was found to decrease as the osmotic pressure of the medium is lowered, that is, the lower the osmotic pressure of the medium, the longer it takes the cell to swell half way from its original volume to its final volume at equilibrium. In order to reach an understanding of this relation, it was necessary to study a wide range of concentrations of the medium—from 20 per cent sea water (20 parts of sea water to 80 parts of distilled water) up to 125 per cent (sea water evaporated to four-fifths of its original volume). In the lower concentrations the velocity constants were determined by swelling experiments, while for higher concentrations the cells were first allowed to swell in dilute solutions and then to shrink in more concentrated solutions, k being determined for shrinking. This procedure was justified by the experiments reported in the preceding abstract, in which it was shown that the velocity constant for swelling and shrinking is the same at a given temperature, provided that the concentration of the medium is the same. When the velocity constants are plotted against the concentration of the medium an S-shaped curve is obtained. At 15° k is over ten times as great in 125 per cent sea water as in 20 per cent. This relation points to some factor modifying the ordinary laws of diffusion. It is believed that this factor is a change in permeability of the membrane to water, this permeability being apparently low in dilute solutions and higher in concentrated ones. A hypothesis is offered of the structure of the membrane that appears to account for this behavior. It is suggested that diffusion occurs through the pores of a partially hydrated gel, which is permeated by the medium and in osmotic equilibrium with it. When the solution is diluted the gel takes up water from it and swells, so narrowing the pores, while the reverse process occurs when a more concentrated medium is used. The egg of the sea urchin has proved to be an excel-

lent natural osmometer which presents many advantages over the artificial osmometers ordinarily employed. By its use we have obtained data on rates of osmosis from which deductions can be made on the mechanism of osmosis, on the laws governing diffusion of water and on the nature of cell membranes.

Investigations on the Ethyl-iodid Method for Determining Cardiac Output in Man.—ISAAC STARR, JR., and C. J. GAMBLE (from the Laboratory of Pharmacology, University of Pennsylvania). In attempting to utilize the ethyl-iodid method of Henderson and Haggard for determining the output of the heart, difficulties were encountered with the analysis of ethyl iodid by the iodin-pentoxid method. Therefore a method was devised for the analysis of minute amounts of ethyl iodid in air, water and blood by means of its reaction with silver nitrate.

Ethyl iodid in air is analyzed by adding standard silver nitrate in nitric acid to bulbs containing the vapor, allowing the reaction to go to completion and titrating the excess silver nitrate. Ethyl iodid is driven from blood by boiling in a vacuum, the vapor being caught and analyzed. The method has an average accuracy of 2.3 per cent for amounts of ethyl iodid in air ranging from 2.5 to 0.1 mg. (maximum error, −5.7 per cent in 20 analyses). Similar amounts in blood have been determined with an average accuracy of 3.4 per cent (maximum error, −6.6 per cent in 9 analyses). As other volatile halogens are not encountered in physiological investigation the method is regarded as determining ethyl iodid alone.

By means of this method the coefficient of distribution of ethyl iodid in air and water has been determined to be 2.7; in air and normal blood *in vitro* at 37°, to be about 7.6, instead of 2 as previously believed. Plasma and anemic blood have a lower coefficient than normal blood.

Evidence has been obtained that the destruction of ethyl iodid in water and blood *in vitro* is a slow rather than a rapid process, and that ethyl iodid is not completely destroyed in the body but is eliminated by the breath (as found by Moore, Hamilton and Kinsman), and so much occur in the venous blood during the inhalation of ethyl iodid.

The fact that the ethyl-iodid method gives figures for bloodflow resembling other methods appears to be due to the fact that these errors tend to cancel each other. In its present form results obtained by this method cannot be accepted.

Cerebral Metabolism and its Bearing on the Regulation of Respiration.—CARL F. SCHMIDT (from the Laboratory of Pharmacology of the University of Pennsylvania). In an earlier report (AM. J. MED. SCI., 1926, **172**, 152) it was stated that the respiratory responses to changes in systemic blood pressure might be explained by a hypothesis similar to that of Gesell (*Am. J. Physiol.*, 1923, **66**, 5); that the tenability of such a hypothesis could be tested experimentally by showing: (1) that activity of respiration varies inversely as cerebral bloodflow, and (2) that the metabolic activity of the medulla is greater during hyperpnea than during quiet breathing. Evidence was presented that respiratory activity does vary inversely as cerebral bloodflow (within certain limits that were not defined). This report is concerned with estimations of the gaseous metabolism of the medulla when respiration is

altered by various means, and with a definition of the limits beyond which a decrease in cerebral bloodflow becomes depressant to respiration.

For this purpose the vertebral arteries of cats and dogs were perfused with the animal's own blood, so that cerebral bloodflow was constant in spite of withdrawal of blood for analysis. Having determined the O_2 and CO_2 content of affluent (arterial) and effluent (vertebral venous) blood, gaseous metabolism could be calculated for the structures drained by the vertebral veins. This included, to a predominant extent, the brain stem, and it is assumed that in a change in indicated gaseous metabolism the central respiratory mechanism participated. Respiration was altered by direct electrical stimulation of the medulla, and by strong stimulation of a central vagus stump or by puncture of the medulla; by inhalation of CO_2 (10 per cent in O_2); by rebreathing; by acute and subacute cerebral anemia; by drugs (caffein, morphin, atropin, cyanids).

The results are further confirmation of the hypothesis: Gaseous metabolism of the brain stem was increased when respiration was stimulated, decreased when breathing was depressed or inhibited. As a rule, figures for O_2 consumption were more constantly parallel to respiratory activity than were those for CO_2 production, but in response to CO_2 inhalation the O_2 consumption of the brain stem was usually decreased, while CO_2 evidently accumulated in the brain. This was shown by: (1) A greater percentile increase in CO_2 content of arterial than of cerebral venous blood; (2) a level of venous CO_2 above normal for several minutes after arterial CO_2 had returned to normal (in these cases respiratory activity corresponded with the CO_2 content of cerebral venous blood). Caffein stimulated breathing and increased cerebral O_2 consumption and CO_2 production markedly (threefold in one experiment). Morphin and atropin, in dosage that caused prompt respiratory failure, reduced cerebral O_2 and CO_2 metabolism very markedly; O_2 consumption was reduced to one-tenth its preëxisting level in one experiment with morphin; the effects on CO_2 metabolism were unique in that, immediately after the drug, CO_2 content of cerebral venous blood was typically less than that of arterial; this effect was not accompanied by increased lactic-acid content of cerebral venous blood, and it is suggested that it was due to liberation of base within the brain cells as a result of the action of the drug. Cyanids reduced cerebral O_2 consumption very markedly, but usually increased the apparent CO_2 elimination from the brain.

With the results of these and the preceding experiments as evidence of the tenability of the hypothesis, it is possible to explain the depression of breathing produced by a rise in blood pressure and the stimulation produced by a fall. The opposite relation—stimulation of breathing with a rise in pressure, depression by a fall—is commonly encountered experimentally and clinically, and cannot be explained by the original hypothesis. It has been found that the respiratory center is rapidly depressed or paralyzed when its oxygen supply is reduced, either by inadequate O_2 tension in the blood or by inadequate bloodflow, or both; CO_2 is purely stimulant to breathing when inhaled for fifteen minutes or more in concentration as high as 80 per cent, provided that 20 per cent of O_2 is present and blood pressure is normal,

but if cerebral bloodflow is reduced during inhalation even of 10 per cent CO_2 respiration may fail abruptly. Respiration may fail as a result of respiratory stimulants (atropin, strychnin, camphor, caffein, CO_2 inhalation, electrical excitation of the medulla), if they are applied when cerebral bloodflow is definitely subnormal. Such "reversal" is accompanied by a marked reduction in cerebral O_2 consumption and by an increase in lactic-acid content of cerebral venous blood, and these return to normal very slowly or not at all; the only possible way of reïnstating respiration under such circumstances is by improving cerebral bloodflow.

This "reversal" is evidently due to an injury to the vegetative functions of the cells of the brain stem (including the respiratory and other medullary centers), evidenced by a prolonged depression of the ability of the cells to utilize oxygen. The damage appears to depend on inadequate oxygen supply to the cells and its precipitation by respiratory stimulants is probably due to the fact that the oxygen supplied to the cells was barely adequate for their needs before they were stimulated, and the stimulus did not increase the oxygen supply while it did increase the oxygen demand.

It is suggested that the nervous regulation of respiration may be exerted through changes in the rate at which the cells of the respiratory center produce chemical stimulant material; that the ultimate purpose of the respiratory and vasomotor centers is the maintenance within themselves of a constant pH or CO_2 tension, this being attained by means of the factors stated in the original hypothesis; that when respiration is stimulated by a rise in blood pressure and depressed by a fall, the center is in a state of depression because of inadequate oxygen supply and respiratory stimulants may be dangerous, the indicated treatment being improvement in cerebral bloodflow by circulatory stimulants or reduction of intracranial tension.

The action of drugs on cerebral metabolism is being investigated.

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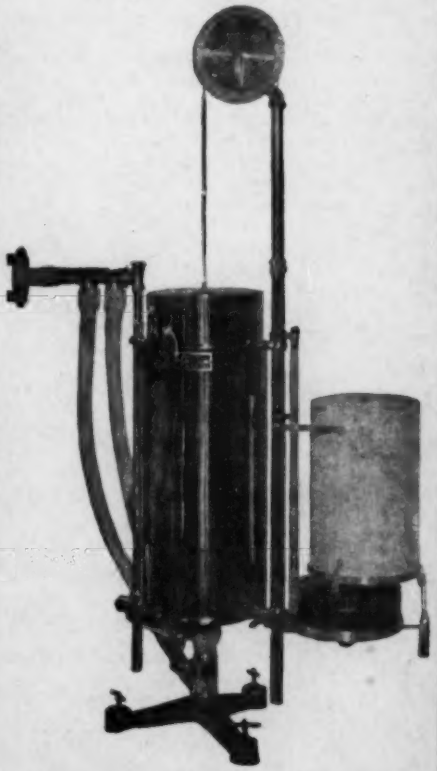

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